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(12) United States Patent

Freije et al.

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(54)	MATERIALS AND METHOD FOR ASSAYING
, ,	FOR METHYLATION OF CPG ISLANDS
	ASSOCIATED WITH GENES IN THE
	EVALUATION OF CANCER

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This patent is subject to a terminal dis-

claimer.

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- (51) **Int. Cl.** *C12Q 1/68* (2006.01)

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USPC 435/6.1; 435/6.11; 435/6.12; 435/6.14

(58) Field of Classification Search

None

See application file for complete search history.

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(57) ABSTRACT

Provided are methods, reagents, and kits for evaluating cancer, such as prostate cancer, in a subject. Disclosed methods of evaluating cancer include methods of diagnosing cancer, methods of prognosticating cancer and methods of assessing the efficacy of cancer treatment. The methods include assaying a biological sample for methylation of a CpG island associated with specified genes. Provided reagents and kits include primers suitable for amplifying at least a portion of a target CpG islands associated with specified genes.

24 Claims, 67 Drawing Sheets

FIG 1A

GAGTTTATTTTCGTTTGCGTGCGATAGGGTTTTTGTATTTAAGTGAGTTAA GGAATGAATTTCGAATTTTTTGGGAAAGTTATTAACGTTTTTTCGTATTT TTTTTAGGGTTTTTGATTACGGAGATTTTGTTTGGGGTATAGGTGTGGGAG TCGTAAATTTTTTTTCGCGTCGTTTTTTTTCGCGTGGAATGGGACGGAGTA GTTTTTTAGGCGTTGTTTGGTTGCGGAGGGGAGCGGGTAGCGAGAGTTT CGGGTTTTCGTTTGGGTTTTCGGGTTTTCGGGTTTTCGCGTAGCGTTTAGCGATTTTTGTCGGGGGTTTTCGGTAGTCGCGTCGTTATTT TTCGTTCGGTTAGCGCGGGAGGAAAAGGGGTTGCGTTCGGGAGCGTCGAG GGAAGAGGGGGGGGGGGGGTTAGGGGAGGGTGCGAAGGAGGCGTTTGT TTTTAATTTGCGGGCGGGAGGTGGTTGCTGGGGGTAATTGAAAAAGAG TCGCCGAGGAGTTTTTCGAAATTTGTTGGAATTTCGGGTTCGCGCGGAGG TTAGGAGTTGAGCGGCGGCGGTTGTCGGACGATGGGAGCGTGAGTAGGA CGGTGATAATTTTTTTCGATCGGGTTGCGAGGGCGTCGGGTAGAGGTTA GGACGCGAGTCGTTAGCGGTGGGATTTATCGACGATTTTTCGGGGCGATA GGAGTAGTTTCGAGAGTTAGGGCGAGCGTTCGTTTTAGGTGGTCGGATCG TTCGTCGCGTTCGCGTCTTTTTTGTAGGTAACGGGAGACGTTTTCGCG TAGCGCGAGCGTTTTAGCGCGGTCGTTCTTTTTTTTTCGAGGGATAAAT TTTTTTAAATTCGATTCGAGTTTTTGGATTAAATTCGTTTGCGTCGAGAGT CGTTCGCGTAGAGCGTTTCGTTTTCGGCGAGATGTTCGAGCGTAAAGAAG GTAGAGGTAAAGGGAAGGTAAGAAGAAGGAGCGAGGTTTCGGTAAGAA GTCGGAGTTCGCGGCGGGTAGTTAGAGTTTAGGTGGGTGCGTAGCGCGGT CGTGGTTTTTTTTTTTTTTTTTTTCGTTCGTTTTTTTCGTTTTTCGTTTTGCA ${\tt GCGTTCGTTGAGTCGCGCGGTGTTTTTTTTTTTTTTGGGGGTCGTCGTTTATTTG}$ GGCGTCGAGTTTATCGGGCGTTTACGTTTAGAGTTTAGGGTAAGGGATA GTAGTTTCGGTCGTATTTTTTAGAGTTTCGGGAGCGTTTCGTTTTTTGGTA CGGTTTTTTTTAGCGTTTTAGCGGTTGAGTTTAGTTCGGGAGTGGGATTT GGGTTATAGGAGTCGAGGTTGCGTGCGCGCGTGTTTCGCGTTATAAGCGT TTTGTACGGGGTCGTGTTTTTTTAGCGGGAAACGTTGGAATGGGTCGTT TGGAGGGAGAGTCGGTTTTTTCGGTGTGTTTTGGTAGCGTAGAAGTGGGTG GTCGAGTAAGAGGTCGCGTGGGAAGT [SEQ ID NO: 1]

FIG 1B

ATTTTTTACGCGGTTTTTTGTTCGATTATTTATTTTTGCGTTGTTAGGTATA TCGAGGGGATCGGTTTTTTTTTAGGCGGTTTATTTTAGCGTTTTTCGTTAG AGGGTATACGGTTTTCGTGTAAAGCGTTTATGGCGCGGGGTACGCGCGTA CGTAGTTTCGATTTTATAGTTTAGGTTTTATTTTCGGGTTTGGGTTTAGTCG ${\sf TTAAGGCGTTGGGGAGGGGTCGTGTTAGGGAGCGAAGCGTTTTCGGGATT}$ GGCGTTCGGTAGGATTCGGCGTTTAGGTGAGCGGCGGTTTTTAGGAGGGG AAGTATCGCGCGATTTAACGGGCGTTTAGAGCGTAGGGCGAAGAGGACG GGCGAGGGAGGGGAGGGAGGAGGTTACGGTATTCGAGGAGGAGGAG GAGTAGGAGGAGGAGGATCGTGGGGTTCGGGTCGCGTTGCGTA TTTATTTGGGTTTTGGTTGTTCGTCGCGGATTTCGGTTTTTTTGTCGGAGTTT TCGTCGGAGACGGAGCGTTTTACGCGGACGGTTTTCGGCGTAGGCGAGTTAGAGCGAGCGTTGAGGCGTTCGCGTTGCGCGGGGGCGTTTTTCG TTGTTTGTAGGGAGCGCGGCGGGCGGCGGCGGCGGTTCGGTTATTTGG AACGGCGTTCGTTTTGGTTTTCGGGGTTGTTTTTGTCGTTTCGGGAAGTC GTCGATGGGTTTTATCGTTGGCGGTTCGCGTTTTTGGTTTTTGTTCGGCGTTT TCGTAATTCGATCGGGGAGAGGTTATTATCGTTTTGTTTACGTTTTTATCG $\mathsf{TTCGGTAGTCGTCGTTTAGTTTTTGGTTTTCGCGCGAGTTCGGAGTTTT$ AATAAGTTTCGGGGAATTTTTCGTCGGTTTTTTTTTAATTGTTTCGTAGTTA TCGCGTTGGTCGGGCGGGGGGGGGGGGGGGGGGGTTGTCGGGAATTTTCGAT AGGGGTCGTTGGACGTTGCGCGGAGATCGAGGTTAGCGTTTCGGAGATTC TAGGTAGCGTTTGGGAGGGTTGTTTCGTTTTATTTTACGCGGAAAAGGAC GGCGTAGAGAAAGTTTGCGATTTTTATATTTGTGTTTTAAGTAGAGTTTT CGTGGTTAGGAATTTTGGGAGGGGTGCGGGGGGAACGTTGGTGGTTTTTT TAGAAGAGTTCGGGGTTTATTTTTAATTTAATTTAAGTATAAAAGTTTTGT CGTACGTAGGCGAAAATAAATTT

[SEQ ID NO: 2]

FIG 1C

ATTTTGGCGTTTAATATCGTTAATATTAGTGGGTTGTTAGGGGGTTTCGTGG GAGGCGTTTTAGTCGGGGTTTTGTTGGCGTTGGCGTTTTGTTATCGTG GGAGGTAATTTGTTGGTTATCGTGGTTATCGTTTGGATTTCGAGATTTTAG ATTATGATTAACGTGTTCGTGATTTCGTTGGTCGTAGTCGATTTGGTGATG GGATTTTTGGTGGTGTCGTCGGCGGTTATTTTGGCGTTGATTGGTTATTGG TCGTTGGGCGTTATTGGTTGCGAGTTGTGGATTTCGGTGGACGTGTTGTGT GTGATCGTTAGTATCGAAATTTTGTGCGTTTTTGGTCGTGGATCGTTATTTG GTTGTGATTAATTCGTTGCGTTACGGCGTATTGGTTATTAAGCGTTGCGTT CGGATAGTTGTGGTTTTGGTGTGGGTCGTCGCTCGCGGTGTCGTTTGCG TTTATTATGAGTTAGTGGTGGCGCGTAGGGGTCGACGTCGAGGCGTAGCG TTGTTATTTAATTCGCGTTGTTGTGTTTTCGTTTTTAATATGTTTTACGTGT TGTTGTTTTTTTCGTTTTTTTTTTTTTTTTTTTTTTTTCGTGATGTTTTTCGTTT ACGCGCGGGTTTTCGTGGTGGTTACGCGTTAGTTGCGTTTGTTGCGCGGGG AGTTGGGTCGTTTTCGTTCGAGGAGTTTTCGTCGGCGTCGTCGCGTTTTTT GGTTTCGGTTCGGTGGGGACGTGCGTTTCGTTCGAAGGGGTGTTCGTTTG CGGTCGGCGGTTCGCGCGTTTTTTGTTTTTTCGGGAATATCGGGTTTTGTG TGGTTAACGTGTTGCGCGTTTTGGGGGGGTTTTTTTTTAGTTTCGGGTTCGGT TTTTTTTTTTTTAATTGGTTAGGTTATGTTAATTTTGTTTTAATTCGTTTA TTTATTGTCGTAGTTCGGATTTTCGTAGCGTTTTTTCGTCGTTTTTTGTGTCG TTGCGGTCGTTGTTTTCGGAGTTTTGCGTCGTTCGTTCGGTTTTT TTTTTTCGGGCGTTTTGCGGTTCGGAGTAGTTTAGCGTAGTTTAGGTTTT GTTAACGGTTCGACGGGTAGGTAATCGGGGTAGAGGGATCGGCGGTTTAG GGTCGGGAAGTATGCGATGTTCGTGGGTTAATTTTTTGAGTGTGGAGTT TATTAAGAGAAGGTGGGATGGTTTTGTTTGGAGAGAAAAGGGAACGAGG TTAGGGTAGAAGTA

[SEQ ID NO: 3]

FIG 1D

TGTTTTATTTAGTGATTGGATTCGGAAAGAAAAGGATTTTGGGTTTTAT TTTGGTTCGTTATTTTCGTTTTTTTTTTTTTTAAGTAAAGTTATTTTATTT TTTTTTAATAAATTTTATATTTAAAAAGTTGATTTACGGATATATCGTATG TCGTTGGTAAAGTTTGGGTTGCGTTGGGTTGTTTCGGGTCGTAGGAACGTT CGAGGGGAAGAGGGTCGGGCGGCGGCGCGTAGGGTTTCGGAGGTAGG CGACGGTCGTAGCGGTATAGAAGACGGCGGAAGGCGTTGCGAAAGTTCG GGTTGCGGTAGTAGATGAGCGGGTTGAAGGTAGAATTGGTATAATTTAGT TAGTTTAGGGTAAGGAAAGTCGGGTTCGGGATTAGAGAGGGGTTTTTTAG GGCGCGTAGTACGTTGGTTAGAAAGAAGGGTAATTAGTAGAGAGTGAAG GTGTTTATGATGAGATTTAAGGTGTATAGGGTTCGGTGTTTTCGGAGAGGT AGGAGGCGCGCGGTCGTCGTCGTAGGCGGGTATTTTTTCGGGCCGGAGC GTACGTTTTTATCGGGGTCGGGGTTAGAGAGCGCGACGGCGTCGGCGGAG ATTTTCGGGCGGAAAGCGGTTTAGTTTTCGCGTAGTAAGCGTAGTTGGC GCGTAGTTATTACGAAAATTCGCGCGTAGACGAAGAGTATTACGAGAAGA GGAAGGTAGAAGGAGACGGAGGAGGATAGTAGTACGTAGGGTATGTTGG AGGCGAAGGTATAGTAGCGCGGGTTGGAGTGGTAGCGTTGCGTTTCGGCG TCGGTTTTTACGCGTTATTATTGGTTTATGATGGGCGTAAACGATATCGCG GTCGATACGATTTATATTAGGATTATAGTTGTTCGGGCGTAGCGTTTGGTG ATTAGTGCGTCGTAACGTAGCGGGTTGGTTATAGTTAGGTAGCGGTTTAC CGTTAAGGTGGTCGTCGGCGGTATTATTAGGAGTTTTATTATTAGGTCGGT TGCGGTTAGCGAAGTTACGAATACGTTGGTTATGGTTTGGAGTTTCGGAG TTTAGGCGATGGTTACGATGATTAGTAGGTTGTTTTTACGGTGGTTAGTA TCGTTAGCGTTAGTAGGGTTTCGGTTAGGGTCGTTTTTTACGGAATTTTTG GTAGTTTATTGGTGTTTGGCGGTATTGGGCGTTAGGGT [SEO ID NO: 4]

FIG 1E

CGAAAAGTTTTTGAGGCGTTGCGTGTATTTTATTTTAGGATATCGTGTGTG CGCGTCGAGTTGAGTGCGAGGAACGTGGCGCGAGGGTCGGGGGATGTCG GGTTGCGTGGGTGTGAGTTTTCGCGCGATCGCGATTTCGCGTTTTTTTCGT AGACGTTTTTTTTAGGTTTTTTTGGGCGTTTATTGTAAATTTTGCGATTAA CGGTTAGGGGAGGAGTTTTTTAATTTCGGAGTTTAGGGAGTCGGGAG TTGTTTCGGGACGAGTTTTCGGAGTTTAGTCGGTTGCGGAGTTTCGGTTC GGGTCGGTTTCGGGGTTTTTTTGTCGGGGTGGGGTGCGAGTTTTTGTTCGA TTTTTTTGGGGCGGTTTAGGTAGGTTTGTCGGTTTTCGAGGAGGTGGTTAG GGCGTTTTGGTTTAGTAGGTTTTTTTTCGAGTCGGGGGGAGGGGAGATCG TAAGCGCGTCGCGGGCGTGAGGGTAAAGTTTTCGAGGTTCGCGCGGAGAG TATACGTGTATGTGCGCGCGGGGTTAGGTCGGGGTCGGTAGGATGCGTTG GTATTATCGGGGAGACGTTTTGTCGGTTTTCGGTTTTTGGGCGTAGGGACGT TTTTTTAACGTTTTGTTTTTCGAGTTTTCGGATGGTTCGGGTTTTACGGAT TTCGCGTTTTTTAGTTTTAGTTTTAGTTTTTTAGGTTTTTTAGATTTAGCGGC GTAGGGGCGGGGTAGGGGTAGTGGGGGTTGGAGGGCGTAGTCGGTTT GAGTGGGTTCGAGTCGTAGTCGGGGGAGTTAGTTAGTTTCGGT TAAGGTAGTAGTTTAGGAAGGGCGGCGATTGAGTCGAGGGAGT CGGCGGTTGGGTTTTTTTTCGGTTCGCGATTTTCGGCGTCGTCGTCGT TATCGTTATCGTTTTCGTTTTGTCGTCGTCGTCGTTGTAGAGTATC GTAGTTTCGCGTTTTCGCGTTTCGCGTTTCGCGTCGTTAGTCGTTTGGG AGTTCGAGCGTCGAGTTCGGGGCGGAGGAGAGGGGGCGTTGGCGCGAGAG AGAGGAGAGAAAGATATACGTACGTAGAGATATACGGTTATTGGAAT TTTATTAGAAAAAAGTGAGTCGAGTAAGGGTTAGCGGGAG [SEQ ID NO: 5]

FIG 1F

TTTTCGTTAATTTTTGTTCGGTTTATTTTTTTTAATGGAATTTTAGTGATC TTCGGCGTTCGGGTTTTTAGGCGGTTGGCGGCGCGGGGCGCGGGGCGCGG GAGCGCGGCGAGTTACGATGTTTTGTAGCGGCGGCGCGATAAGGCGA AGGCGGTGGCGGTGGCGCGGCGGCGCGCGTCGGGGATCGCGG TGGGATTGATTTGTTTTTGGTCGGAAATTGATTGGTTTTTCGGTTACG AGTTTTTTTTTTTTGGGGATCGGTTGCGTTTTTTAATTTTTATTGTTTTTGT TTTCGTTTTTTGCGTCGTTGGGTTTGGGAAGTTTGGGGAGTTGAGTTGAGG TTGGAGGCCCGGAGTTCGTGGGGTTCGAGTTATTCGGGGGGTTCGGGGGG TAGGGCGTTAGAAAAATTTTAGTCGGTGGTTCGGGTTTGAGGGGGGGTTTT ATTTTTCGTGGGTTAAGGCGTTTTTGCGTTTAGGAGTCGAGGTCGATAAAG CGTTTTTCGATGGTGTTAGGGAAAGGAATTATTTTTTCGGCGTCGGTTT CGCGCGTTTTCGAATTTAACGTATTTTGTCGGTTTCGGTTTAGTTTCGCGC GTATATATACGTGTGTTTTTCGCGCGGGATTTCGGGAATTTTGTTTTTACGTT CGCGGCGCGTTTGTTTTCGTTCGTTTCGGTTTTTATTTTTTCGAGATGTTT TTTTTTTGGTTGGGAAGAAGTTTGTTGGGTT TAGAGGAATCGGGTAGGGGTTCGTATTTTATTTCGGTAGGAGGGTTTCGA GATCGATTCGGGTCGGGTTTCGTAGTCGGTTGGGTTTCGAGGAGTTCGTT TTAGTCGGGAAGGGGCGATTGATTTATTTGTCGGTGGGTCGGGTTTATC GGCGTGTTTTAGTCGTAGAATTTATAATAAACGTTTAGAAGGATTTAAAA GGAAGCGTTTGGTTGGGAAAGGGTTGGAGGAGAGGTGCGGTTA CGTTTCGGCGAGAGCGGGAGAGGCGCGGGGTCGCGCGAGGGTT TATATTTACGTAGTTCGGTATTTTTCGGTTTTCGCGTTACGTTTTTCGTATT TAGTTCGGCGCGTATATACGGTGTTTTGGGGTGGGGTATACGTAGCGTTTT AGAAATTTTTCG [SEQ ID NO: 6]

FIG 1G

GAGGTATTAGTTTTTGAAGGTTTATTTTTAATATTGGTTGCGAGAGTAAG AATGGTGTGAATTTATAAAAGTCGTTATTGTTGTAGGTAAGTTGTAGTAA ACGATTCGCGTTCGAGTATTTTCGTTTTCGTTTTCGTTTCGTTTCGTTTAC GACGATTTTGGGGAATTATAAGTTTCGTTATATAGCGGGGAGCGTTCGGA GTTCGCGTCGGTTTCGTTTTTAGTTCGGTTTTTATTTTCGGTTTCGTTTTCG GTTTTTTTCGTCGGGTTAATTTCGAAGAGTCGTCGGTGGTCGCGGTAGAC GGAAGTCGAACGAGTTTTTCGGCGGTTGTAGGATGGGGGATTTTAAAGTG AAAGTGGCGGTGCGGATACGATTTATGAATCGGCGAGGTGAGAGTCGAG TCGGTCGTCGGGGGGTTCGGCGGTTTCGTTTTTATAGTTAGCGGCGGGG CGCGAGGAGGGGTTCGGGGATTTTGAAATTCGTTTTCGCGTTGAGACGTT CGGTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTGGTTAGTTTCGTTTTTTGGCGTCG TCGGGTTTTCGTGTCGGTTTCGTTTTTTTTCGTTTGCGTTCGTTT TTGCGTTTTTTTGTTTTTTCGTTTTTTTCGGAGGTTTTCGAGGGCGTTTTCG TTGTTATCGTCGTTTTCGCGCGCGGGTCGTTAGTTTTTGTAGTTCGTTTCGG GATCGTTCGGGATTTTCGGGATTTCGCGTTTCGTTCGGGTCGTTTAAGTT TGTATCGTTTTGGTTCGCGGCGGGAAGAAGGGTAGGGGGTTAGGCGGGTG TTTCGCGGCGAGTTTTTTTTTTTTTTTGGGCGTTTTGAGATTGGGGTTAGGTGG AGGAGATGTTTTTCGTTGTTTTTGGATAGTTGAGAAAGTTTTGGTTTTGT TTGAAGTTTTATTTTTTTAATAAATAGTTAAAGTGTTAAGATTTTT **GTGGAATTGTATTTTTTTGATA** [SEQ ID NO: 7]

TGTTAGAAAGATATAATTTTATAAGAATTTTGGTATTTTAGTTATTTG AGAGATGATGAGATTTTAGGTAAAATTTAAAATTTTTTTAATTGTTTA AAAATAACGAAAAGGGTATTTTTTTTTTTTTTTTATTTAATTTTAGGACGTTT GTTTCGGGGGGTTTCGAGGCGGTTGTAGGGGTTGGCGAT TCGCGCGCGGGGGCGACGATGATAGTTGGCGGGGAAGGAGCGAGGTTGA GGGGTTAGGACGAGGTTGGGCGCGAGGGTCGAGGGCGTTTTCGGGAATTT GCGGAAGGGGTAGCGGGTCGGTACGAGGGGTTCGACGGCGTTAGGGAC GGGGTTGGTTAGGGGGGAAGGGAGGGAGAAGAGGGAGTCGGGCGTTTT AGCGCGGGAGCGGTTTTAGGGTTTTCGGGTTTTTTTCGCGTTTCGTCGT TGATTATAGGGGGGGGTCGTCGGATTTTTTACGGCGGTCGAGGGAAGGG CGCGTTAGGTATTTGTCGTTTCGTTTCGGCGGTTTAGGAGGGTTCGGTTT TTATTTCGTCGGTTTATGGGTCGTATTCGTATCGTTATTTTATTTTGGAGT TTTTTATTTGTAGTCGTCGAGGAATTCGTTCGGTTTTCGTTTGTCGCGGTTCGGGGGTGGGATCGGGTTGGGGGCGGGGTCGGCGCGAGTTTCGGGCGT TTTTCGTTGTATGGCGGGATTTGTAGTTTTTTAGGGTCGTCGTGGGCGGG TCGTAGCGAAGGCGGGGGGGGAATGTTCGGGCGCGAGTCGTTTGTTATA GTAGTTAGTATTGAGAAGTAAGTTTTTAAGAGTTGATATTTT [SEQ ID NO: 8]

FIG 1H

TTGTGGAGCGGAGGAGGGGGGGGGGTTTCGT TTTGATCGTAGAGTTTTTTTTCGAGGAAAGCGGTTGGTTCGGTTTCGGTT TTTCGTTGCGTTTCGGATAGTTTGGAGGTGAGTACGCGTTGGGTTTTGGAT CGCGAGTAGCGGGAGAAGTACGAGTTGGTGGTCGTGTATCGTGTACGT CGGCGCGCGAGGAGGTGTGATGGTGTTTTTTTCGGTGATCGTGTACG ACGAGGACGATTCGGCGTTTATTTTTTCGCGGGCGTCGATATCGTTAGCG TCGTGGTGGAGTTTAAGCGGAAGGAGGTGTTTGTTCGCGCGTGTTGTGGT CGTGTAGTTATTTAATCGTGTGGTCGATTATTCGCGTTTTTATTTGTTTTTC GTTTTCGTTTGCGTCGTTTGTTTTAGGGGGAGGGGAAGGGGGAGTTTTGTT AGTATTTAGTTGGGTTTTGTTTCGGGAGGTAAGGATTAGGACGAGGTTCG TAGTTTTTAACGGGAGGGTTTTTGAGTGATTACGAGTAGAGTCGGGGATT TTCGGTTCGCGTTGGTGGAGCGCGATCGTTATTTGTTGG

[SEO ID NO: 9]

TTAGTAGGTGGCGGTCGCGTTTTATTAGCGCGAGTCGGAGAAGGGCGGGG CGGGCGCGTCGGAGGTGATTCGTTTTTTCGTTTTTTTTTAATTTTCGGTTT TGTTCGTGGTTATTTAAGGGTTTTTTCGTTGGGGGGTTAATTGTTGGTGGGA GGGAGTGTTTTTCGGTAGATGTTTTTCGTTCGGGTAGCGCGTCGCGTTCG TTTGTAGCGGTATAAGTATGTTTTAGACGCGAGTTTTCGGGTTTCGTTTTG TTTTTTTTTAGGATAGACGCGTAGACGGAGGCGAAGGATAAATGAAA GCGCGAATGGTCGGTTATACGGTTGGGTGGTTATACGGATATTAAATCGA TCGAGAAACGAATTGTGGTCGGAGATAGATATTGGGTAGATTATAGTACG CGCGGATAAGTATTTTTTTCGTTTGAATTTTATTACGGCGTTGGCGGTGT CGACGTTCGCGGGGAAGGTGGCGTCGAGTCGTTTTCGTCGTATACGGTT ATCGGGAAGGGTATTATTATTATTTTTCGCGCGCGCGTCGGCGTGTACGGTG TATACGGTTATTAGTTCGTATTTTTTTCGTTGTTCGCGGTTTAGGGTTTAGC GCGTGTTTATTTTTAGGTTGTTCGGGGCGTAGCGGAAGGGTAGATTTTTAT TTGCGTATTAAGTAGATAGGGGTTTCGCGTGATTATTAGTCGGGATCGGG TTAGTCGTTTTTTCGGGAAGGGGGTTTTGCGGTTAGAGCGGGGCGTATAT CGTCGCGGTTTTAGGTTTTTTTTTTTTTTTTATAG

[SEQ ID NO: 10]

FIG 1I

TTTCGCGGTAGGTTTCGTTGTATCGTGTATTTTTTTCGCGAGAAGTTGATTT TGCGGAAGGCGTTCGTTATTATCGTCGTTATTTGGCGTTTTTGGCGTTGTTTA TTATGTGTTTTTCGGTCGTTACGTTGATCGTTATTCGTGAGGAGTATTATTT TGGTTCGAGAAGGGTATGCGTAGGGTTTATATTATTGTGTTTTTTTCGTAT ATTTATTTGGCGTCGTTGGCGTTTATCGTGGTTATGTACGTTCGTATCGCG CGTAAGTTTTGTTAGGTTTCGGGTTCGGTTTTCGGGGGCGAGGAGGTTGCG GATTCGCGAGTATCGCGGCGTAGAGCGCGCGTGGTGTATATGTTGGTTAT GGTGGCGTTGTTTTTACGTTGTTTTGGTTGTCGTTTTTGGGCGTTGTTGTTG TTTATCGATTACGGGTAGTTTAGCGCGTCGTAGTTGTATTTGGTTATCGTT TACGTTTTTTTTCGCGTATTGGTTGGTTTTTTTAATAGTAGCGTTAATT TTATTATTTACGGTTATTTTAACGAGAATTTTCGTCGCGGTTTTTTAGGTCGT TTTTCGCGTTCGTTTTTGTTCGCGTTCGTCGGGGAGTTATAAGGAGGTTTA TTTCGAGCGGTTCGGCGGGTTTTTGTATAGGCGGGTTTTCGTGGTGGTGCG GTTTAGCGATTTCGGGTTGTTTTTTGAGTCGGGTTTTAGTAGTGGGGTTTTT AGGTTCGGTCGTTTTTCGTTGCGGAAT

[SEQfIDNO: 11]

ATTTCGTAGCGGGGGCGGTCGGGTTTGGGGGTTTTATTGTTAGGGTTCG ATTTAGAGGGTAGTTCGGAGTCGTTGGGTCGTATTATTACGAAGATTCGTT TGTGTAGAAGTTCGTCGGGTCGTTCGGAGTAGGTTTTTTTGTGGTTTTTCG ACGGCGCGGTAGAGGCGGCGCGGAAGGCGGTTTGGAAGTCGCGGCG GAAGTTTTCGTTGAAGTAGTCGTAGATGATGGGGTTGGCGTTGTTGA AGAAGGTTAGTTAGTGCGCGAAGGGGAAGGCGTAGACGGTGATTAGGTG TAGTTGCGGCGCGTTGAGTTGTTCGTAGTCGATGAGTAGTAGTAGCGTTTA GAGCGGTAGTTAGGATAGCGTGAAGAATAGCGTTATTATGATTAGTATGT GTATTACGCGCGTTTTGCGTCGCGATGTTCGCGGGGTTCGTAGTTTTTTCGT TTTCGGGGGTCGGGTTCGGGGTTTGGTAGAGTTTGCGCGCGATGCGGGCG TATATGATTACGATGAGCGTTAGCGGCGTTAGGTAGATGTGCGAGAAGAG TATAGTGGTGTAGATTTTGCGTATGTTTTTTCGGGTTAGGTTTTTTAGTAG GAGTAGAGCGGTAGGAGCGGTTGCGGGCGTTTATTATGAAGTGGTGTTT TTTACGGGTGACGGTTAGCGTGACGGTCGAGGGATATATGATGAGTAGCG TTAGGGTTTAGATGACGGCGATGGTGACGAGCGTTTTTCGTAGGGTTAGT TTTTCGCGGAAAGGGTGTACGATGTAGCGGAATTTGTCGCGGGGAGAGAG ATAGGCGGGATTTGGGTGGGTTTTTAGGGTTTTTTGCGAGGGGACGGT [SEQ ID NO: 12]

FIG 1J

TTAGTTTCGGTCGTATTGTATAGCGAGGTCGGTTCGGAGTTCGGATGTTGG GAAGTCGGGTTAGCGGGTGTCGCGGGTAGTCGGCGTTCGGGACGGGGTGT GGCGTTTAGAGCGTTGTTTTTTCGTAGTTAGGAGGTTGGATGTCGGGTT TGGGTGTTTTTTAGAAGGAGTCGTATTAGCGACGAGGGAAGAGGAATTGG TTTTTCGGGTAGTTTTTTCGTTTTAAATTTTTTTTTTTCGCGGAGGGTGGG CGGGCGGAGGAGGAAGCGTAGTCGGGGAACGTGGCGTTCGCGTTTTTTT CGTTCGGGGTTGCGTTGGGTTGAGTGTTTTTAAATTTGAGTTTTTCGGATTGGCGGTCGGGTCGGGTTCGTTTTTCGGCGTTGGGTAGCGGGGCGTT GGGGAGTAGCGCGCGTACGGGTCGGGGCGCGTAGGTTTCGTCGTCGG TGAGTACGGGTTTTTTTCGCGTGGTTTCGTCGGGTTCGTTTGGTTTGTTTA TTTTCGGAGTTATTTTTGTTTTCGTATGGGTTGGCGAAGTTGGGAGGAGCGAGTTGGAGTTAGAGCGCGCGTCGGGCGCGTTTCGTCGTTGTTTGATTCGGC GTTCGTAGTTCGGGCGTAGTACGTCGGTCGTAGGAGTACGGATGTTTTTCG GAGTCGCGGGTTGGTAGGTATCGAAGTGTTTTGTTTTGGGGTTGGCGAGG GGAGGGTAAATTTGGAATTTTTCGGGTATTTTTTAGTTCG [SEQ ID NO: 15]

FIG 1K

TAGGGTAGGATATTTCGGTATTTGTTAGTTCGCGGTTTCGGGGGGGTATTCG TGTTTTTGCGGTCGCGTGTTGCGTTCGAATTGCGGGCGTCGAGTTAGGTA GCGACGGGCGCGTTCGGCGCGCGTTTTGGTTTTAGTTCGTTTTTTTAAT TTCGTTAGTTTATGCGGGGGTAGAGGTGGTTTCGGAGGTGGGTAGGTTAG GCGGATTCGGCGAGGTTACGCGAGAGGGAGTTCGTGTTTATCGGCGACGGGATTTGCGCGTTTCGGTTCGTGCGCGTCGCGTTGTTTTTTAGCGTTTCGTTA GCGTTACGTTTTCGGTTGCGTTTTTTTTTTTCGTTCGTTTATTTTTCGCGAG TTTCGTCGTTAGTGCGGTTTTTTTTGGAAGATATTTAAATTCGATATTTAGT TTTTTGGTTGCGAGAGGTAGTAGCGTTTTGGGCGTTATATTTCGTTTCGGA TATAGTTAGGTCGAGTTTCGGCGGGATCGAGTTTAGTATTCGGGTTTCGGG TCGGTTTCGTTGTGTAGTGCGGTCGGAGTTGG [SEQ ID NO: 16]

FIG 1L

TTTCGCGGTAGGTTTCGTTGTATCGTGTATTTTTTTCGCGAGAAGTTGATTT TGCGGAAGGCGTTCGTTATTATCGTCGTTATTTGGGTTTTTGGCGTTGTTTA TTATGTGTTTTTCGGTCGTTACGTTGATCGTTATTCGTGAGGAGTATTATTT TGGTTCGAGAAGGGTATGCGTAGGGTTTATATTATTGTGTTTTTTCGTAT ATTTATTTGGCGTCGTTGGCGTTTATCGTGGTTATGTACGTTCGTATCGCG CGTAAGTTTTGTTAGGTTTCGGGTTCGGTTTTCGGGGGCGAGGAGGTTGCG GATTCGCGAGTATCGCGGCGTAGAGCGCGCGTGGTGTATATGTTGGTTAT GGTGGCGTTGTTTTTACGTTGTTTTTGGTTGTCGTTTTTGGGCGTTGTTGTTG TTTATCGATTACGGGTAGTTTAGCGCGTCGTAGTTGTATTTGGTTATCGTT TACGTITTITTTCGCGTATTGGTTGGTTTTTTTAATAGTAGCGTTAATT TTATTATTACGGTTATTTAACGAGAATTTTCGTCGCGGTTTTTAGGTCGT TTTTCGCGTTCGTTTTTTTTTCGCGTTCGTCGGGGAGTTATAAGGAGGTTTA TTTCGAGCGGTTCGGCGGGTTTTTGTATAGGCGGGTTTTCGTGGTGGTGCG GTTTAGCGATTTCGGGTTGTTTTTTGAGTCGGGTTTTAGTAGTGGGGTTTTT AGGTTCGGTCGTTTTTCGTTGCGGAAT

[SEQ ID NO: 11]

ATTTCGTAGCGGGAGGCGGTCGGGTTTGGGGGTTTTATTGTTAGGGTTCG ATTTAGAGGGTAGTTCGGAGTCGTTGGGTCGTATTATTACGAAGATTCGTT TGTGTAGAAGTTCGTCGGGTCGTTCGGAGTAGGTTTTTTTGTGGTTTTTTCG ACGGGCGCGGTAGAGGCGGGCGCGGAAGGCGGTTTGGAAGTCGCGGCG GAAGTTTTCGTTGAAGTAGTCGTAGATGATGGGGTTGGCGTTGTTGA AGAAGGTTAGTTGCGCGAAGGGGAAGGCGTAGACGGTGATTAGGTG TAGTTGCGGCGCGTTGAGTTGTTCGTAGTCGATGAGTAGTAGTAGCGTTTA GAGCGGTAGTTAGGATAGCGTGAAGAATAGCGTTATTATGATTAGTATGT GTATTACGCGCGTTTTGCGTCGCGATGTTCGCGGGGTTCGTAGTTTTTTCGT TTTCGGGGGTCGGGTTCGGGGTTTGGTAGAGTTTGCGCGCGATGCGGGCG TATATGATTACGATGAGCGTTAGCGGCGTTAGGTAGATGTGCGAGAAGAG TATAGTGGTGTAGATTTTGCGTATGTTTTTTTCGGGTTAGGTTTTTTAGTAG GAGTAGAGCGGTTGCGGGCGTTTATTATGAAGTGGTGTTT TTTACGGGTGACGGTTAGCGTGACGGTCGAGGGATATATGATGAGTAGCG TTAGGGTTTAGATGACGGCGATGGTGACGAGCGTTTTTCGTAGGGTTAGT TTTTCGCGGAAAGGGTGTACGATGTAGCGGAATTTGTCGCGGGGAGAGAG ATAGGCGGGATTTGGGTGGGTTTTAGGGTTTTTGCGAGGGGACGGT [SEQ ID NO: 12]

FIG 1M

TGGTTACGAAGAATCGGTTGGTTACGTCGAAGATGTTTATTACGTTTCGTT GGGTAGGTGATTTTTGGTTTATTTCGTTTTTCGGTTTGTTCGTTTTCGGGGA TTTTATTTTTGGGGTGGGGTTGGGGATAAAGGGTTAGGGTTTTCGGCGTAG TCGTTTTTAAGGGTTTTTAGAGTTTAAGTTGTTTTTTAGGGTTTTCGGAGTT TAAGTTTGCGTTAGTTTAGATTAGTTTGTTTTGTGTAGGGGATTTTCGGCGG TCGTATTTAGTTTCGGATTTTTAGACGCGAGTTCGATTTTAGCGGTTTTTTA GTTTGGGTTAGGTCGGGGCGCGTGTTTCGGGTTTTTTGTGGTTGTATCGCG CGTTTTGTGTTTACGGGCGAAGGCGTTGGAATTCGGCGTTCGGAGTTCGA GTTTTTGAAGGCGGGAGGCGCGTTCGATTTTAGGGGTTGCGTTGGGTTG TCGGAGTTAAGAGTGTTTGCGTTTTTAGTTTCGCGTTAGAAGGGATCGGA GTTCGAGTTCGGTTTTCGGGGTTTTCGAGTAGGTGTTCGTCGAGGG TTTTAGAGTGTGATTGAGCGGGTTGGTTCGGCGGTCGTTGTTTTCGTTTT CGTTTTTTCGCGTTTGGTCGCGTTATTTATTGTCGCGGGTGTTCGCGTGCGC GTCGTCGATGCGGTCGTCGGGGAGCGTTTGGAGGTGGAAGTCGATGTTTA CGTCGTTTTGGACGGTCGTTTTTTTGGGTTGCGTTGTTATCGGTAGGCGCG TTAACGAGAGCGTTATTAGGTTTTTTTAGCGGCGTTTTTAGTTCGGTTTTTA GCGTGTCGTTGGGTGTAGTGGGTGCGGCGCGTTTTTTCGGTTCGTTTAGG GCGTTAGTAAGGTTAGTAGGATCGTCGGGAGTAGCGTTATCGCGGTCGTT TCGGGTTTCGATATTTCGGTTCGAGGGTCGTGCGTCGGTTAGGCGGTTAGT GCGTTCGGGAAGTTGGGGGGTAGAGTTGCGTTTGTGGCGTTTCGCGGGAG CGTACGGTCGATTTCGGGTAGGAGTGCGTAATCGAGGAGGTGCGGGAGGT AAGCGACGGGTTTTCGGGCGTCGGGTTTTATTTCGGTTGTATGGAGCGG CGAGTCGGGCGAAAGCGCGCGGTTGGAGTTGGGATTTTGAGGAGTAGT AGTTCGGCGTTTTTTTTTTATTCGTTCGTTTTCGCGGGGGGTCGTTCGCGTTT TTTTGGGCGTTCGGGGCGTTGTGGCGTTCGCGGTTGGTCGTAGGTCGTTTG TTAATTAGGGTCGGGGAAGGGAGGAGGTTGGGGATTAGCGTCGCGAGT GTTTTTTGTATTTTGTTTT

[SEQ ID NO: 20]

FIG 1N

AGGGTGAAGTTTGAGAGTTTAAATGGTTAATTTTATAGGGTTGAACGTTTT AGAAGTCGTAGGTTCGTTGGGGTTGATTTTGGTAGTTGTCGTGGAGGTGG GGGTATTGTTGGGTAACGGCGCGTTGTTGGTCGTGGTGTTGCGTACGTCG GGATTGCGCGACGCGTTTTATTTGGCGTATTTGTGCGTCGTGGATTTGTTG GCGGTCGTTTTATTATGTCGTTGGGTTTGTTGGTCGTATCGTCGTTCGGGT CGTCGTTTTGTTGTCGGTTTGTACGTTCGGGGTGGTCGTATTTGGTTTGGT ACGTTATCGTTTTATCGTGTATTCGTTGCGGTTAGGTTCGCGGTCGTCTT GTGTTCGTGTTTATCGTCGTGTGGGTCGCGGGGGATTGTTGGGCGCGTTT TTTGGTTGGGGGTTTCGGGTTTTTCGGTCGTTTTGGGTTTTC GCGTTGTTCGTTTTTTTGTTGTTCGGCGTTTTACGGCGGTATTTTCGTGGTGG CGCGTCGCGTTGTTTTGAGGTTTTTACGGTCGGCGCGCGGGTTTCGATTTT TTTGTTCGGGGGTAAGGCGGTTTTGGTTTTAGCGTTGGTCGTGGGTTAATT TGTAGTTTGTTGGTTGTTTTATGGTTGCGCGTGTTTGGCGTTCGTAGCGCG GGTCGCGGAAGTCGAAGCGGTTGTTATTTGGGTCGTTTATTCGGTTTTCGC GGTTTATTTTTTTTGTACGGGTTGTTGTAGCGTTTCGTGCGTTTGGTATTG GGTCGTTTTTTCGTCGTGTATTGTTTGGATTTGTGCGGGTTTGTATTTCGT AAGTTTGGTATTCGCGGGTATTTTTGTAATGTTTTTAGAGATTTTTAGAGG GTTTTGTCGTAGGTTTTTTGAGGTTTTAGAATAGATTTTCGAGTTGGTAG GAGGGCGGAGTTTCGTATATT

[SEQ ID NO:21]

AGAAGGGTTTACGGTAGGGTTTTTTGGGGGGTTTTTTGGAGGTATTGTAAGA GTGTTCGCGGGTGTTAGGTTTGCGGAGTGTAGGTTCGTATAGGTTTAGGTA GTGTACGGCGAGAGAGGCGGTTTAGTGTTAAGCGTACGGGGCGTTGTAGT AGTTCGTATAGGAAGGGTGAGTCGCGAAGGTCGAGTAGGCGATTTAGGT GATAGTCGTTTCGGGTTTCGCGGTTGCGGGCGTTAGGTACGCGTA GTTATAAGGTAGTTAGTAGGTTGTAAATTGGTTTACGGTTAGCGTTGGGGT TAGGGTCGTTTTGTTTTCGGGTAGGCGAGGTCGGAGCGGCGGTAAGATGG AAAGGCGGTTATTTAGAGAGTTCGAGTGGAGTCGGGATTCGCGCGTCGGT CGTGGGGGTTTTAGGGTAGCGCGACGCGTTATTACGAAGATGTCGTCGTA GGCGTCGAGTAGGAGGGCGGGTAGCGCGAAGGTTAGTAGGGTTTAG AGCGGTCGGAAGGGTTCGAGGTTTTTAGTTAGGATCGAGTAGCGAGTAGG AGTAGGGGGGGGGGGGGGGGTGTCGAGTAGGGAGAGCGCGTTTAGT AGTTTCGTCGCGGTTTATACGGCGGTGAGTACGAGTATAGGCGGCGGTCG CGAGTTTGGTCGTAGCGGGTGTACGATGAGGCGGTAGCGTGTTAGGTTAA GTGCGGTTATTTCGAGCGTGTAGGTCGGTAGTAGAGCGGCGGAGAGGAA GCGAGCGCGCGTATGGCGCGGGTTTAGGCGTACGCGGTTTAGTTCGG GCGCCGTTCGTTAGTAGGTTTAGCGGTATGATGGAGGCGGTCGTTAGT AGGTTTACGACGTATAGGTGCGTTAGGTAGAGCGCGTCGCGTAGTTTCGG CGTGCGTAGTATTACGATTAGTAGCGCGTCGTTGTTTAGTAGTGTTTTTAT TTTTACGATAGTTGTTAGGATTAATTTTAACGAGTTTGCGATTTTTGAGGC GTTTAGTTTTGTGGAGTTGGTTATTTTGGGTTTTTAGGTTTTATTTT [SEQ ID NO: 22]

FIG 10

GGGATGATAAGGGAGAAAAATTTTTTTACGGTTTCGTTTGGTTCGCGGCG TTTGTTTGCGCGGGGTTAAAGTTCGGCGTCGTTTACGCGCGGTTCGG AGCGTCGGGGCGTTACGTTCGAGGTCGCGGGGTCGGGGTTGTAGGTATAG CGGTATCGTCGTCGGAGTCGTAGCGAGTTTTTAGAGTTTGGTTGTTGG CGGTCGGGACGTCGGGACGGGCGCGAAGTCGGAGGTTTCGGGACGTG GATATAGGTAAAGGTCGGCGGGTCGGAGTCGGGCGGGGCGCGCGGCGG CGTTTTCGGAGGGATTTGGTTCGGTCGGGTTTTATTTAGTCGCGGTGGT TCGGGTTTTTACGTTGGTTTAGGCGGGGACGTGTTAAGGGGTTTGGTTAG GGTTGTCGTTGGTCGTTTTTCGTTCGGCGGGTTTTAGGTGACGCGG TCGCGGTTTAATTTTCGTATTTGAGGTTTTCGGAGCGGTTTCGGGGCGCGTTTATTTGGAGGTTGGAATTATATAGGGTCGAAAAAGTTGAGTTTTGGAGG TTAGGGGTTTAGTATTGAATTTTTTTTAGGTTTGAGGTGGGGAATTGCGTT TTTTTTGTACGGTTTTATTTTTTTTTTTTTTTAGT [SEQ ID NO: 25]

FIG 1P

ATTGAAATGGGTTAGATAAAGGAAAGTGGAATCGTGTAGAGGGAATCGG TCGTGGAAGGGGTTGTGTGGTTTTTATAAGTTTCGAAATTAAATAAGACG TAGTTTTTATTTTAGATTTGGAGAGGGTTTAGTATTGGATTTTTGGTATTT ATTTTATTTTTCGGTTTTTTCGTTATATTTATAGCGTTTCGTTTTTAGGA TTTAGTTTTTCGATTTTGTGTAATTTTAATTTTTAGGTGGGCGCGTTTCGA GGTCGTTTCGAGAGTTTTAGGTGCGAAAGTTAAGTCGCGGTCGCGTTATTT GAGGTTCGTCGGCCGAGAGGCGGTTAGGTTAGCGGTAATTTTAGTTTAGT TTTTTGGTACGTTTTCGTTTGGGTTAACGTGGGGGTTCGGGTTATCGCGGT TGGGTAGGGTTCGAGGTTAGGTTTTTTCGAGAGGCGTCGTCGTCGC GTTTCGTTCGATTTCGTCGGTTTTTATTTGTATTTACGTTTCGGAGT TTTCGGTTTCGCGTTTCGGCGTTTTCGGTCGTTAGTAGTTAGGTTTT GAGGATTCGTTGCGGTTTCGGCGGCGGCGATGTCGGTTCGGCGAGACGGG AAGCGATAGGAGTTAAATTTCGCGGAAAGCGTTCGAGTTGTGTTTGTAGT AGCGGTTTTGTTCGTTTTACGTTTGCGGGTTTTTATTCGAGTCGCGCGTGG GCGGCGTCGGGTTTTGATTTCGCGTAGGTAGATAAGCGTCGCGGGTTAGA [SEO ID NO: 26]

TGAGGTGTGGGATTATTTATTTCGGTGGGTTTTTTTATTTTAGGTCGGTT TTTTATTACGCGTGGGTGTGGGGGTATTGTTTTCGTTGCGCGTAGGAATA GCGGGGAGAGTTAGGAGCGGAGCGGTTTCGGGATGTTAGATTGAGTAGT GGGTTCGTTTGCGGTTATTTTTTAGGGAATAAGTTTTTTTCGCGGAGATT TTGTTTTTTAAAAGTTTTTTTGGGTTTAGTTTAGGGCGATAGGACGATTT AGTTTTTTTTCGTTCGGGGCGCGCGTATTTTAGCGTCGCGGGTTTAGCG TTTAGTAGTCGCGTTTTAGGTCGGGTTTCGGGGAGTTCGTAGGCG CGCGTTCGGTCGGGCGTGTCGGGAGCGCGCGGCGGTCGGGGGCGGAGCG TAGTTAGGGTTGCGCGGCGCGTTTCGGTTTTCGTTCGTTTTTAGTCGGGTT CGCGGGGGTCGAGTCGCGAAGCGCGTTTGCGATTCGGCGTTCGGGCGCGT TGGAGAGGACGCGAGGAGTTATGAGGCGTTAGTTTGCGAAGGTGGCGGC GTTGTTGTTCGGGTTGTTTTTGGAGGTAGGGGTCGGGGATCGGGTGTTGTC GGAGGCGCGCGTTTATTATGTTGGCGGTTGGGGGCGCGTAGTTTCGAGG CGTTTTAGAGGATTTTGTTTGGGAGCGTAGACGGTGGAGCGACGGGGAGT TATAGTTTTGCGCGTTTTTCGGAGTTGGGAGGTGCGGGATTTTGGTGACGG GGAGGTTTTCGTTTCGCGTTTTTCGTCGTTTTTTCGGTTTTTCGTATT TCGTTTTTATTTTGCGGGTGAGCGCGTTTTTCGCGTCGATCGTTTTCGTTAG GAGGATCGGATGGATTCGGGGTTGGCCGGGGGTGGTTTTCGGGCGCGCG TAGGCGCGGAGAGTTCGGGGCGTCGGGTAGTTTGGGGTTAGGAAAGGAT GGGTGTCGAGTCGGGGTGAGGGGAGCGGGGGGGGGGATTGTGGGGAAG TGTCGCGGGAGTGTCGGGAGTTGTGGAGTGAGTAGCGGGAGGAGGCGT TTTCGCGTGTGAAAATGAAGTGTAGTTTTTAGGTGCGGGGAGGAAATTTT GCGGAGAGTTTGGTTGGGTGGGGGTGCGGAGTCGAAGTCGCGGGGAAT TTGTTGAGCGGTTTTCGGGTGCGAGCGTTCGTGATCGT

[SEO ID NO: 27]

FIG 1Q

GCGGTTACGGGCGTTCGTATTCGGAAGTCGTTTAATAAGTTTTTCGTCGGT ATTTTATAATTTTCGGTATTTTCGCGATATTTTTTATAGTTTTTTCGTTC GTTTTTTTTATTTCGGTTCGGTATTTATTTTTTTTAATTTTAAATTGTTCGG CGTTTCGGGTTTTCGCGTTTGCGTCGAGGATTATTTTCGTTTAAT TTCGGGTTTATTCGATTTTCGGTTTTTTGCGGCGGGGAGAGGGGGCGGAC GGTGTATAAAGGTTATTTCGAGTTAACGGAGGCGGTCGGCGCGCGGAAACG CGTTTATTCGTAGGGTGGGGGGGGGGGGGGGAAAATCGAAGGAACGACGG AAGGCGCGGATCGGGGCGGGAGTTTTTTCGTTATTAGGGTTTCGTATTTTT TAGTTTCGGGAGGCGCGTAGGGTTGTGGTTTTTCGTCGTTTTATCGTTTGC GTTTTTAGGTAAGGTTTTTTGGGGCGTTTCGGAATTGCGCGTTTTTAGTCG TTAGTATGGTGGGCGTCGCGTTTTCGGTAGTATTCGGTTTTCGGTTTTTATT TTTAAGAGTAGTTCGAGTAGTAGCGTCGTTATTTTCGTAGGTTGGCGTTTT ATGGTTTTTCGCGTTTTTTTTAGCGCGTTCGGACGTCGGGTCGTAGGCGCG TTTCGCGATTCGGTTTTCGCGCGGGGGGGGGGGGGGTAGATTGTAGTCGGGA GGCGCGTCGCGTAGTTTTGGTTGCGTTTCGTTTTCGGTCGTCGCGCGTTTT CGATACGTTCGGGCGCGCGTTTGCGGGTTTTCGGAATTCGAGGTTC GGTTTGGGGCGCGTTGTTGGGCGTTAGGTTCGCGACGTTGAGGTGCGCG CGTTTCGGGCGGAGGAGGGGTTGTATCGTTTGGCGAATGGGAGGGGGAT TGGTAGGTTTTTTTTTTAAGGGAGGTCGTTTTGTCGTTTTAGATTAAATT TTGAGAGGTGGTCGTAGACGAATTTATTGTTTAGTTTGGTATTTCGAAGTC GTTTCGTTTTTTCGTTGTTTTTTGCGCGTAGCGGGGGTAGTGTTT TTATATTTACGCGTGATGGGAAGGTCGGTTTGGGGGGTGGGAAGGTTTATC GAAATAGATGGTTTTTATATTTTA [SEQ ID NO: 28]

FIG 1R

AATTTAGAAATAAATATATATGTATACGTATATAAATATATTTTAA CGAAGTAAATTATGGGATGTTATTTACGTTTGTTTTAAAGGTATCGAATTT ATAAATTATTTTAGGTGCGGAGTAGGATAGGTTGAAAATAGGAATGATAT GAATTCGCGCGGAATAGTTGTCGGCGCGGTGTTTAGGGCCGGTATTTCGTT CGGTTTCGGTTTTTTAGTTTTGGGTTCGATTTTTATTACGTTTTTGTTTCG ACGCGAACGCGGAGTTCGAGCGCGCGTTACGTCGTGTGGGGTCGAAGAG GTTGTTATTTAGAGGCGGAGTGCGGGTTCGCGAGGGTTTTTATTCGATTTT AGTTGGGTGGAAGTAGCGCGGATTTACGGTATATCGAACGTATTTTAATA GAATTCGACGTAGATACGCGTTTTTAATCGGCGGAGATATTGGTAGGGTT AGAAACGCGCGTAGCGGGGGGGGGGGGGGGTGGTAAGTTTTTCGTTTTTGTT CGTACGGGTTTCGTTTTTCGCGCGACGTTTTTTGTTGATTCGGAAACGGAT TTTTCGGAGTCGAGGTTCGTTCGGGTGAGTGTTTTTCGTTTTTTGTGGTTAA ATTTAGTTACGTAGTTTTTTTTTGCGGCGTTTTTTATATTCGGGGTTTGTT GGTTTTCGCGGATGTTATAGGTTCGGTAATCGTTTTTTTGTCGGCGGGGAG TTTCGCGACGTTCGGAAATGTTTCGAAGTTTGTCGTTTAGTTGTTAGATTT GCGTTTGTGTTCGGTTTCGTTATTGAGGTCGTTTTTGTTCGGTTTTTTTATT TTAGTTTTTTTATCGTTCGTTTATTTTATCGCGCGCGGTTTTAGGTTTCGA TTCGGTATGTGGTTTGTTTTTTATCGTTTT [SEQ ID NO: 29]

GGGACGATGGAAGATAAGTTATATGTCGAATCGGGATTTGAGGTCGCGCG CGATAGGATGGGCGGACGGTGAAGAGAATTAGGGTGGAAGGGTCGGATA GGGGCGATTTTAGTGACGGAATCGGATATAGACGTAGATTTGGTAGTTGG GCGATAGGTTTCGGAGTATTTTCGGGCGTCGCGGGATTTTTCGTCGATAGG AGGGCGGTTGTCGAGTTTGTGATATTCGCGGAGATTAGTAGATTTCGGGT GTGGAGGACGTCGTAGGAAGGGAATTGCGTGGTTTGGGTTATAAAA AGCGGAGGGTATTTATTCGAGCGGATTTCGGTTTCGGAGAATTCGTTTTCG GGTTAATAAAAACGTCGCGCGAGGGGCGGGGTTCGTACGTGTAGGGAG GGGAGGTAGAGAAAAAGGCGGGGTCGGGTCGGGCGGGGTTTCGGGTAG TTAGTGTTTTCGTCGGTTGAAAGCGCGTGTTTGCGTCGGGTTTTGTTGGAG TAAGAGGCGCGTGAGGTTTTTGTGTCGGGGGCGGTGTTGTTTTCGAGTCG GCGCGCGGGGGACGCGAGTTCGTAGGTGTTGGCGGGAGCGAGAGTCG GGTGGGGATTTTCGCGAGTTCGTATTTCGTTTTTTGGGTAGTAGTTTTTTCG GTTTTATACGGCGTGACGCGCGTTCGGGTTTCGCGTTCGCGTCGAGGTAG AGGCGTAGTAGGGTCGGGTTTAGGGTTGGAGGGGTCGGGATCGGGCGG GGTGTCGTTTTGGATATCGCGTCGGTAGTTGTTTCGCGCGGGGTTTATGTTA TTTTTTTTTTAATTTGTTTTGTTTTCGTATTTGAGATGATTTATAAATTCGG TTTAAATGTAATATATTATTATTTAAAAGTATTTTTAATTTGAAATAT ATTTGTATACGTATATATGTATATTTATTTTTTGAATT [SEO ED NO: 30]

FIG 1S

TGCGCGTTGTTGCGTTGAGGTCGAATGAAGCGTAGTACGGTGCGGGTAGT TCGAGGTTTCGAGGTTTGGTTTGTTTGGGATTGCGTCGTGTTTAGT TTCGGTTTTTTTTTGTGGGTAAGGATGGTTGAGTTTAGTTTTTACGGTAGC AGATTGGATTTTTTTTTTTTTCGCGTTTTTTTTTTCGTATTTTTTATTCGTT GGTTTTTTTTAGTTGTTTTTTTTTTAGGTTTTTTTTTGGTTGCGCGCGTTTT GTTCGGTCGGCGTTTCGTTTTCGCG TTCGGAGTAGTTTAGTTTTGTAGTGGTTCGGGATTCGATGTTATGAGAGGG AAGCGAGTCGGGCGTTTAGATTTTTAGGAGGCGTCGGATGCGCGGCGGGT TTTGGGATCGGGTTTTTTTTCGGTTCGTTTTGTTTTCGGGTGATTATTTGG TGGAGTATTTGTAGATATGATTGCGTGGAGGAGATTTTAGTCGTTGTTTTT GTTTTTCGGGTTGTTGGTGTTGTGCGCGAGGTTTTTTATTGTAGCGAAGGG TAAGACGGATTTGTTTTTGGTCGGGGGGGGGGTAGAGTTTTCGGAGGTTT CGTGTGCGGACGCGAGTGTGCGTTTTGGGGATCGTAGGGTACGGAGTGGT CGTTTTTGTTCGGCGTTGTTTTATCGTCGAAGTTCGGGGAACGCGATGTAC GGGAGGGAGTTTTTATCGCGTTTTTTTAGTTTTTTTGGGTTTTCGTTTTAT GTAGTATAGGGTGTTAAGGAGAAAGGAATTTAATACGAGTTGGGTTGGAA TTGTGTTCGTCGGGGCGGTGTTGTTTTTTCGAGACGTGGATTTTACGGG TCGGGGTGGTTGAGGGTAGTTTTTAGGATTTTTTTTTCGGATTCGACGCG TTTGGGAAGCGTTTCGGGTGAAGTCGGTTTGGAAAGTTCGGGTTTTTTACGGGGGTTTTGGTATTAATAGGTAAAGGTTTTCGTCGGTTCGGTTTTTTCGT ATTTATATTTTTTTTTTTTTTTTTTTTTTTTAACGTTTTTAGTCGG **TCGTTTTT**

[SEQ ID NO:31]

FIG 1T

AAGGAGCGAAGTTCGGGGGGGGAGAAGCGGGGGGGGGATTTTTTAGAGGT AGTTATTTTCGTCGGTTGAGGACGTTGGAGAGGAGGAGGAGGAGGAG GAATGGGGTGTATGGGTGCGAGGAGGTCGGGTCGGCGGAGATTTTTGTTT ATTGGTATTAAAATTTTCGTAGAGAGTTCGAATTTTTTAGGTCGGTTTTAT TCGGGACGTTTTTTTAGGCGCGTCGGGTTCGGGGAGAAGTTTTGGGAATTGTTTTTAGTTATTTCGATTCGTGGAGTTTACGTTTCGGAGGAGGTAATA TTGATATTTTGTCGAGAAAAAGAGATTTTTTTTTGTGAGTTTAAGAG AGGGGGAAGGAATGGCGGGGTGGGGCGGGGTTTAGGAGGGTTGGGGAG AGCGCGATGGAAGTTTTTTTTCGTGTATCGCGTTTTTCGAGTTTCGGCGAT GGAGTAGCGTCGGGTAGAGGCGGTTATTTCGTATTTTGCGGTTTTTAAAAC GTATATTCGCGTTCGTATACGGGGTTTTCGAGGGTTTTATCGTTTTTTCGGT TAGGAGTAAGTTCGTTTTATTTTTCGTTGTAGTGAGGAGTTTCGCGTATAG TATGTTTGTAGATATTTTATACGTACGCGATATCGATGGTTTTTTCGAGGA AGGTAGGGTTATGAGCGGAGTTAAATAATTATTCGAGGGTAAGGCGAGTC GGAGAGAGAGTTCGGTTTTAAGATTCGTCGCGTATTCGACGTTTTTTGAAG GTTTGGGCGTTCGTTTTTTTTTTTATAGTATCGGGTTTCGAGTTATTG TAGGGTTGAGTTGTTTCGAGCGCGGAGATTCGGGTTGGCGGGGTCGGGGT CGGGGACGAGCGTCGGTCGAGTCGGGTAGGAAGGTATTAAGGCGGCGAG GTTGCGGGAGGGGAGAGCGGGGAGAGCGCGCGTAGTTAGGAGA GGGAGGGGGGGGGGGGGGAGAGATTTAGTTTAGAGAGAAAAGG CGGAGAGCGTAGAAGAAGGGTTGTTAGTGGTATAAGGAGTCGTTGTCGTG GAGGTTGGATTTAATTATTTATTATAGAGAGGGGATCGAGGTTGGGT ACGCCTAGTTTAGATAGATAGAGTTTAGTTTCGGGGTTTCGGGTTGTTC GTATCGTGTTGCGTTTTATTCGGTTTTAGCGTAGTAGCGCGTA **ISEO ID NO: 321**

GATTTTTTGGGTTAGGATATGTGAGAGTTGCGTAGGTTTGGGTTCGGCGTG GCGGAGGTGCGCGAGAGCGGTTAGAAGAGGGCGTTAGAGAGTTAGGCGC GGTTCGCGGAGGAGTTCGCGTCGGTTTTTATATTTAGTTTCGCGTCGCGCG GATTTATCGAGTTCGCGTTTAGACGTTTTAGTTTTATCGAGAGGTCGTTCG GGTCGTGTTTTTTTTTTTTTTAGGTGTAGGTAGAGTTTTCGAGTTATGGTT AGTTTTTCGGTAGTTTCGAAGTTATTGGTAAGTTTCGAGGTAGGGATGGT GGTTGTAGTTGGAGGGGGAAGCGTATAGTTCGAGGATTGCGAGAACGG GGAGGACGCGTCGCGGTTAGGTAGGGAGGAGATCGGTATTTAGATAGGT GGCGATCGTAGAGGAGTAAGTGACGCGGGCGTTGGGGTTCGGGGGTGTC GGGGGCGTCGGTAGGGGCGGCGGGAGGTTTCGTGGTCGGTTTCGGGTTGA AGTTGGTATTTTAGCGGTAATTTCGAAGGGCGCGGAGTGATAGCGCGTGA CGGTTTTCGAGACGTTAGTTGTCGTTTTTCGGTTGTGGTTTTTGATTTTT GATTTTTTACGACGTCGTTGGTTGGGAGATTTATTGGATTTTGCGGTTGG TTAAAAAGAGAGGGTAGTTTCGCGTTTTGGGGGTTTTTAGTAGGGGAAG TTGGTGTTTTTTTTTGGCGAGGGGTTAGTGGTGGGGGTAGGGGG[SEQ ID NO: 33]

FIG 1U

TTAGATAGATGTTTTAGATAGGATGTTTAGCGTAATATTCGTTATTTTTTT AGTTTAGTGGGTTTTTTAGTTAGCGACGTCGTGGGAGAATTAGGAAGTTA AAGTTATATAGTCGAGAAGCGGTAGTTGGCGTTTCGGAGGTCGTTACGCG TTGTTATTTCGCGTTTTTCGGAGTTGTCGTTAAAATATTAATTTTAATTCGG ${\tt GGTCGGTTACGGAGTTTTTCGTCGTTTTTTATCGGCGTTTTTCGGTATTTTCGG}$ CGGTTTTTTTTTTTGTTGGTCGCGGCGCGTTTTTTTCGTTTTCGTAGTTTTCG GACGTCGTTTTTTTTTTTTTGGGTCGGTTATTTTTGTTTCGGGGGTTTGTTA TATTTGGAGAAGGAAGGATACGGTTCGAGCGGTTTTTCGGTGGAGTTG AGGGGTCGCGGGTTTTTTCGCGGGTCGCGTTTGGTTTTTTGGCGTTTT TTTTTGGTCGTTTTCGCGTATTTTCGTTACGTCGGGTTTAGGTTTGCGTAGT TTTTATATGTTTTGGTTTAGGAGGTT

[SEQ ID NO: 34]

 ${\sf TCGGCGTTTAGGTGACGTTGATTTTGTTGGTTTATCGTTTTGGGGGGTTATTT}$ AATTTTTTAGCGATGTTTTTTAGTTGGGGAGGTTAAGAAGTGTTTCGTTTA GTTAGGGAGTCGTTAAATAGTAAGATCGCGCGTTTTGCGGTTTTAGAGTG CGGATTTCGGTCGCGTGCGGTTTTGATCGCGTCGTTTTATTTTTGGCGGGG ATTTTTCGGGGTTTTGATTGTTTTTGAGTTTTTTTGCGGGGGGGCGTGCGC GTCGGGCGGGGGGGGGGGGGGGATAAAGGCGCGGGGTTTGGTTGCG CGGGGTTTGCGGTAGTTTTAATTTTGGGTTCGTAGTTTGCGTTGGGTGCG TAGGAAGGTTAGTGTGGGGGTCGTTCGATATTTTTTTTCGCGGAGGTGGG AGTCGAGTTATATTTTGGAGTGGGGATTGGTCGCGGAGCGGGTTGTTTAG GGTCGGTCGAGGTCGGGGCGAGTTTTGCGCGGCGTTGGAGATTTTGTATT TTCGGGCGCGTAGGGTTTTCGGTCGTGGTCGTAGAGTTAGGAGGGGCG GTTTCGGAGTTCGGCGCGGGGAGGGTTTAGGCGTAGTCGGGGTTGGTAGG GCGCGATATTCGTTTTTTTTTTTTTGAAAGGGTTTTTTACGTCGAGAAG AGGGCGGGTATGGTCGGTTCGGCGAAATCGGTTTGTATAGATTTTGGGA AGTTATCGTTTGCGGAGGGTGGGATTTTATAGTTTGTTTATTTGTTTAGGT TGAGATTTCGTGTTTTAGTTTTGGATGTTTTACGGGTTTTTCGTTTCGGGTA GATTTTTTTTAGTTTAGGTTTAGAGTTTTGGG

[SEQ ID NO: 35]

FIG 1V

TTTAAAGTTTAAGTTTGAGTTAGGGAGGGTTTTAGAGGGAGGTTTGATTG TAGATCGGGAGTTTTTTTTTTTCGTGCGTCGTTGTTCGGGACGAGAAATTC GTGGGGTATTTAGGATTAGGATACGAGGTTTTAGTTTGGGTAGGTGGATA AGTTGTGGGGTTTTATTTTTCGTAGGCGATGGTTTTTTAAAGTTTGTATAA ATCGGTTTCGTCGGGTCGGTTATGTTCGTTTTTTTTTTCGGCGTGGGAAGTT TTTTTAAAAGTGGAGGGAGCGAGTGTCGCGTTTTGTTAATTTCGATTGCG TACGGTCGGGGATTTTGCGCGCGTTCGGGAATGTAGAGTTTTTAGCGTCG CGTAGGGTTCGTTTCGATTTCGGTCGGTTTTGGGTAATTCGTTTCGCGGTT AGTTTTTATTTTAAGATGTGGTTCGGTTTTTATTTTCGCGGGGGGAAATG TCGGGCGATTTTTATATTGATTTTTTTGCGTATTTAGCGTAAATTACGAATT TAGAGTTGGAGTTCGTAGATTTCGCGTAGTTAGATTTCGCGTTTTTAT TTCGTTTCGTTTCGTTCGGCGTATTAATTTTCGGTCGAGGAGGGGTCGCGTGGCGTCGCGGGGGGGGCGGTCGCGTACGTTTTTCGTAGGGAGGATT TAGGGATAGTTAGGGTTTCGGGAGAGTTCGCGCGCTATCGTTCGGTTTCGC GGCGTTAGTTATGGCGTTCGTGCGTGGTTTCGTTAGGGATGGGGCGACGC GGTTAGAGTCGTACGCGATCGAAATTCGTATTTTGGAGTCGTAGAGCGCG CGGTTTTGTTGTTAGCGGTTTTTTGGTAAGTGACGTGGGGAAGAACGTA GGGCGTAGGAGAGATAGTTGGAAAGGTTTGCGGTGTAGTTGGTTTAGGAT TGAGGGTTTGGAGGTCGGGTGTTGGAAGATTTTGAGCGAGGTATTTTTTG GTTTTTTAGTTGGGAGGTATCGTTGAAAAATTAGGTGATTTTTAAGACGG TAGATTAGTAGAGTTAGCGTTATTTGGGCGTCGG **ISEO ID NO: 361**

AAAGTTAAGCGTCGTCGTTATTTAAGGTATTGCGTTGATGCGTTGCGGGTC GATTAGGTGTTTTCGTCGGGGCGTTTTTTTTTTACGTAGGAAGGGTTACGTC GAGAGAGGTAGGTAATAAGGGTACGGTTGGAGGTCGGAAGGTTATTTCGT TTTCGGCGGGGCGCGCTTTAGTTTTATTTTTCGGGTACGTTCGGGCG GGGCGATTGTAGGGAACGGGGGGGGGGGGGGGGTAGTTTTCGGTTTCGTCG CGCGTTAGTTCGTTGTTCGGAGGCGTCGTAGGTTTGGGTTTTCGGATAGTTGAGTTCGAGCGTCGTTTTTCGAAAGGTGAAGGCGGTTCGGGGAG GCGGGGACGGTGACGGGGCGGGGGGGGGGGGGGTTTTTCGACGGTTGT CGCGGGGTTAGTTTAAAGTTTTCGATTTTCGGTAGTTGCGTTTTTCGCGCG GGGCGTCGGAGTAGGGCGGGTTAAGTTGGTTTGCGGTCGCGGCGGGAAG AAGGGTTAGCGAAGTATTTTCGATCGGGTTTAGGCGTCGGACGTCGGGGG GCGTTTCGTTGTAATTTTTTTTGGAAGTTTCGATACGAGTTTCGGTTCGCG TTTTTCGTTTATTTTTTTTTTTTTTTTTTTTATATTTTAAAAATAGGTTA AGGGGTGGAAGTTATATTTGGTGTAGTTTTCGGTTTTGATGTAAAAGTAGT TTTTGTTTTTGGTTGCGGGATAGCGTTGTGATTATTCGTAACGGGAGAGTT GTTGTTAGTCGTTATATCGTGCGGAAAGCGTCGGCGATCGGAGTATTGAT AATGGTTTGTATAGGGGAGCGGAGAGAAGTTTTTGTTGCGTTTTAGATTC GTTGTTTCGGCGTTCGTTCGTAGGGAGGAGGGGGCGCGATAGGTCGTTTA GCGCGTGTTTCGGAGTTCGCGTTCGGGTTTGGTCGTTTTGGTCAGTTTTTG TTCGTTTTTTTTTTTTTTTTGTAAATAG TTTTGTAATACGATTAAAAATAGGCGAGATAGTTA [SEQ ID NO: 37]

FIG 1W

TGGTTGTTTCGTTTTGATCGTATTGTAAGGTTGTTTGTAAGGTAAAT GCGGTTAGATTCGGGCGCGGGTTTCGGGGTACGCGTTAGACGATTTGTCG CGTTTTTTTTTTTGCGGGCCGGCGTCGAGGTAGCGGATTTAGGGCGTAA TAGAAGTTTTTTTCGTTTTTTTATGTAGATTATTGTTAGTGTTTCGGTCGT CGGCGTTTTTCGTACGGTGTGGCGATTGGTAGTAGTTTTTTCGTTGCGAGTAGTTATAGCGTTGTTTCGTAGTTAGGGGTAAAAGTTGTTTTTGTATTAGAG TCGAGGGTTGTATTAGGTGTAATTTTTATTTTTTGATTTATTTTAGAGTGTG AGGATGAAAGGAAGAGGAAAAAATAGACGGAGGGCGCGCGGGGGTGCG ${\tt GTTCGTGTCGGGGTTTTTAAAGAGAAGTTGTAGCGAGGCGTTTTTCGGCGT}$ GTCGTAGGTTAGTTTGGTTCGTTTTATTTCGGCGTTTCGCGCGGGAAGCGT AGTTATCGGGGATCGGGGGTTTTGGGTTGGTTTCGCGATAGTCGTCGGGA GATCGTTCGCGGTTTTCGTTTTCGTTTTCGTTTTTCGGGTCGTTT TTATTTTCGGGAGGCGCGTTCGGGTTTAGTTGTTCGGGAATTTAGGTTT GGAAGTGAGGTTGGTCGCGTTCGTTCGTCGGGGACGGGGTGATTTTTC TAGGAGAAGACGTTTCGGCGGGAGTATTTGGTCGGTTCGTAGCGTATTAG CGTAGTATTTTGGGTGACGACGACGTTTGGTTTT [SEQ ID NO: 38]

FIG 1X

TATATTTTATTTGTGTCGTATATGTGAAGATATAATTGTAAATCGTTTACG ATTTTGAGTTAAGATTTTGAGTTTTTTGAGGTTAGGAGATCGTTAGGGAAT TAGTAGCGGCGCGGTTTTAGAGAGTTTCGTATTCGGTCGCGTTTTAGTTA CGTTGATTCGGTTGTTCGTAGTGTCGCGTTGTCGCGTAGTTAGGTGTCG TCGGGTTGGCGCGGTTATTTATGATTGCGTGGTTGGGTTGGGGGTTCGGG GTCGGGGAGTAGTCGGGATTCGTCGTTTTTTTATGATTTTTTCGGGTCGA ATTACGGGATCGTTGCAAGGTGGCGTCGCGGGTTTTCGGGGTCGCG CGAGTGTAGGGGTCGTTTTCGGTCGGTCGCGAAGTTCGCGGTATCGATTTT TTTTTTAGTTTTGGTGTGGGCGGTTTTCGTTATGGTTGCGTTGCGAAGGTTT TGGGTCGTGGGGCGGTTTGCGGTGATTATTTTGGGTTTTTTTGGTCGGTT TTTTTTTTCGAGAGGATGAGGAGGGTTGTGGCGGAGGCGGTATGGA GGCGCGGCGCGTTGGGGGGAGTTGAGCGTGGCGGCGGCGGTCGGCG GGGGTTGGTCGGTATGTTATTAGTTGTACGGGGATTTTAGGGTCGG TTCGTCGGCGATCGGGCGATTTTTAAAGAGCGCGGTTACGGAGTTCGAGG ATTCGTTTCGCGGTCGGGGGATGTTGTTTATTTTAGTGGCGGTTGTTAAGG AGACGGTGAGTGCGCGAGCGCGCGTTATATTTGCGCGGGGGATGTGATTT TCGTGTCGGGTACGTAGGATTTTGGAGGTTGTGGGGACGGTGTAAGCGTTGTGGTCGCGGGTGAGGAATTTTTCGTGAGCGAGGTTGATATTTAGGTCGG ATAGTTTAGGATTCGGTTATTTACGTATTGGGA [SEQ ID NO: 41]

FIG 1Y

TTTTAATACGTGGGTGATCGGATTTTAGGTTGTTCGGTTTAGGTGTTAGTT TCGTTTACGGGAAGTTTTTATTCGCGGTTATAGCGTTTGTATCGTTTTTAT AGTTTTTAGGGTTTTGCGTATTCGGTACGAAGGTTATATTTTTCGCGTAGG TGTGACGCGCGTTCGCGTATTTATCGTTTTTTTGGTAGTCGTTATTGGGAT GGGTAGTATTTTCGGTCGCGGGGCGGGTTTTCGGGTTTCGTGGTCGCGTT TTTTGAGGGTCGTCGGCGAGTCGGTTTTGGGGTTTTCGTATAG TTGGTAGTATATTAGGTCGATTAGTTTTTCGTCGGTCGTCGTCGTTACGTTT AGTTTTTTTAGCGTCGTCGTCGTTTTTATGTCGTTTTCGTTATAGTTTTTTT TTTATTTTTCGGGAGGAGGAGGTCGGTTAGGAAGGTTTAGGGTGGTTA TCGTAGGTCGTTTTTACGGTTTAAGGAGGGGTTGGTGAGCGTAGAGTGGA GGAGATATTCGGGGTGGCGGTTATAAGAGTTTTCGTAGCGTAGTTATAGC GGAGGTCGTTTATATTAGAGTTGGGAGGGGGTAGAGAACGGAGGGGCGG GGGCGGGGGGGGGTCGTCGAAATTTCGCGAGAAGTCGGTGTCGCGAG TTTCGCGGTCGGTCGAGAGCGATTTTTATATTCGCGCGGTTTCGGGGATTC GCGACGTTATTTTTAGCGTAGCGGTTTCGTGGTTCGGGTTCGGGAAGATTAT GGAAGAGGCGCGGATTTCGGTTGTTTTTCGGTTTCGAATTTTTAGTTTAA TTACGTAGTTATAAATAATCGCGTTAGTTCGGCGATATTTGGTTACGCGAT AGCGCGATATTGCGGGTATAGTCGAGTTAGCGTAATTGAGGCGCGGTCGA GAGTTGGGTTTAGCGTTCGTTTGGGATATTTATATTTTTTAACGGTTTTTTG ATTTTAGGAAATTTAAGGTTTTGATTTAAGGTCGTGAACGATTTGTAATTG TATTTTTATATATACGATATAAATGAGGTATA [SEQ ID NO: 42]

FIG 1Z

FIG 1AA

CGTTTGCGGAGGATTGCGTTGACGAGATTTTTATTTATTGTTATTAATTTG TGGTGGAATTTGTAGTTGTATATTGGATTTGATTCGTTTCGTTTCGAATGA GATATAAATTAGTACGCGGTCGGAGAATTTCGTAATTTTTGCGTTTATA AAATATATCGACGATGTTCGATTTATTTTAAGGGTTGAAATTTACGGGTTT GAGAGATTATAAGAGCGTTTTTTATCGTTATGGAATAACGGGGATAGAAC GTTTCGGTCGTTTCGGGGGTTCGGAAAAGGTACGGTTTAGGATTTAGGGA GGCGCGGGGAGTTAGGTTTGGGTTTCGGGTTTTTAAGATTTTTGTGTTCGT GAAGAGCGTGTTTGGCGTTTGGAGAGGGTAGGGAGAGAGGGGGATACGG CGGGGGTGCGTTCGGGTCGTTTGCGGTCGGGTATGTTCGGGTAAGAC ${\tt GTATTAGTCGTCGGAGTCGGGGGAAGAGAGATGGGTTTTCGGGTTGGGTAGG}$ AGCGATTTGGGTCGTTAGGGAATAGAGCGCGCGTTTTATTTGGTGTAAAT TTTCGAATTTAGTGGGGGAGGGCGATAAGGAGGGAATTTTCGAGTAAGTT GTTTAGTTTTGATTTTTTTTTTTTTTTTTCGAATGAATTTTTA AAGGCGTTTATTGTAGATCGTTTTGAATTTGCGGTCGGCGAAGAATTTTTT TGTGGTCGTTGCGGTTTAGTGGTTTCGTTTCGTGCGCGGAGTCGTCGCGG GCGTAGTTGGAGAGGTTTTTTTTTTTTTTTTTAGCGGTTGCGTTTTTACGCGTG CGGGGTCGTTTATCGTTAATGTTATTGTTTGGGGTTTTTTTGGGAAAACGAG ATTTAGGAGAAGGGAGTTGTGGTATTTG [SEQ ID NO: 47]

TAAGTGTTATAATTTTTTTTTTTAAATTTCGTTTTTTTAAGGAATTTTAAA TAATGGTATTGGCGATGAGCGGTTTCGTACGCGTAGGGGCGTAGTCGTTA AGGAGGGGAAGGGTTTTTTTAGTTGCGTTCGCGACGATTTTCGCGTACG TAGGTTTAAAGCGATTTGTAATGAGCGTTTTTAGGAATTTATTCGAAGGCG GGAAAGAAAGAAAGAAAAGAGAAAAGAAATAGAAAGTAAGGA AAGAAAATAAAATTAAAGTTCGACGATTTTTTCGTGGTTTTACGTAGTTTA TTCGGGAATTTTTTTTTGTCGTTTTTTTTTTATTGGATTCGGGAATTTATAT TAAGTGGAGCGCGCTTTTGTTTTTTGGCGGTTTTAGGTCGTTTTTGTTTAAT TCGGGGATTTATTTTTTTTCGATTTCGACGATTGGTGCGTTTTGTTCGGA GCGGGGATTTATTAATAGTAGGATCGCGGCGATAACGAGTATAAGGGTTT TGGGGATTCGGGGTTTAGGTTTGGTTTTTCGCGTTTTTTTGGGTTTTTGGGTC GTGTTTTTTCGGGTTTTCGAAGCGGTCGGGGCGTTTTGTTTTCGTTGTTTT ATGGCGGTAGGGAACGTTTTTATAGTTTTTTAGGTTCGTGGGTTTTAGTTT TTAAAGTAGATCGGGTATCGTCGGTGTATTTTGTGGGCGTAGAGATTGCG GGGTTTTTCGGTCGCGTGTTGATTTATGTGTTTAGGTTGATTTGGGGCGGC AAGAGTTTCGTTAACGTAATTTTTCGTAAGCG

[SEQ ID NO: 48]

FIG 1BB

TGTACGTTTATTGTTTTTTTTTTTTTTGTACGTTTGGTGGGTTTTATTTTAG GCGGGTGTTGCGACGGTGGTTATTGCGTTTTTGCGTACGCGGGGGTAGTTT TCGTCGTTATTTTTTTGGCGTATATGTTGAGTTTTTATCGCGATTCGTTGT CGGATTCGGGAAGTGTTGTGGGTTTGGGGTTTCGAGTCGGGTTT GTAGTCGTTCGGGCGTTTCGAGTTTAGGGTTTAGTTTTGCGGGTGTTTTCG CGTTAGTAGGTTCGGGGTGTAGCGTTGGTGGTTGGGGGGCGTATTTACGGTCGAGTCGGGAAGGGATTTTAGCGTTTAGGGTGTGTTTTCGACGGGGATTATTGTTTTGGGTTTTGGGATTGCGCGGAGCGTAGCGCGGAAGGGT ${\tt GGGAGTTTTAATTTTAGTTTTGTGAAGTTGTTTATTTCGGAGTTTGGGTT}$ TGCGTATTTGTAGGATAGGTGTAATAAATAATATTTCGTTTATTAGATTGT GGAAAGCGCGAGATGATAATGCGCGCGAAACGTTTAGCGTAGTATTCGGT ATAGTTATAGTTAACGGTCGTTGGTATTATTGTAATGGTTTTGGCG CGGGAGTATCGGTAGTTGAGTTGGTAATATCGGGGATTCGGGTTTACGGT TCGGAGATTAGGGATGGGTTGTTTCGAAGTCGCGAATTGTGGTAGTTTTG GGTTTTTTAGTCGCGTCGGGGAAGTGTTAAGTGTTTCGTTTAATTTCGGGT TCGGGGTTATGATTTGTAGGGGGGTGTGTTAAGGACGGTAGGGATTTG AGGGTATCGTTTTCGAGGATTTGGTAGCGCGTTTTTGGGTATTTAGCGCGGC GAGTAGGTGGGTGTTGCGGAGAGGGAGTTTTTTTCGCGTTTTAATTTATAT TAGACGGTTTTTTTGGGGTCGGGGCGTAATTTATAAACGTTAATTTGATT CGATTTGTCGTTTGTTTTTTTGTGATTTGGTGTCGGGGGTTTTTCGTTT TCGCGTTTGGGGTTAGATAGTCGGTGATTTTTTTCGGAAGGGTTATTTGGGGATTAGTTAGATTAGGGGATATTTTCGGGGGGGGGGTAATGAGAAATTTG TTGGAGTGTTCGGTTTTTTAATCGAAAA [SEQ ID NO: 49]

FIG 1CC

TTTTCGGTTGAGGGGTCGAGTATTTTAGTAAATTTTTTATTGTTTCGTTTTC GAGGGTGTTTTTGGTTGGTTGGTTTTTAGATGATTTTTTCGGAGAGGGT TATCGGTTGTTTGATTTTAGGCGCGGGAGCGAAGGGTTTTCGGTATTAGGT TATAAGGGCGGTAGGCGGTAGGTCGGATTAGATTAGCGTTTGTGGATT $\tt GTGGGCGGTCGCGGTTGTTTAGGCGGTAGAATGTGGATTGAGGCGCGGAA$ GGGGTTTTTTTCGTAGTATTTATTTGTTCGTCGCGTTGGGTGTTTAGAAC GCGTTGTTAGGTTTTCGAGGGCGATATTTTTAGATTTTTGTCGTTTTTTGATA TTTATTTTTTGTAAATTATGGTTTCGAATTCGGGGTTAAGCGAGATATTT GATATTTTTCGGCGCGGTTGGAGGATTTAAGGTTGTTATAGTTCGCGATT TCGGGATAGTTTATTTTGATTTTCGGGTCGTGAGTTCGAATTTTCGATGTT TTATTCGTAGAAAGAAAAAAAATCGTTAAGATTAAATTATTATAGTAAT ATTAACGATCGTTGATTGTGGTTGTCGGGTATTGCGTTGAGCGTTTCGC TATATTTATATAGATGCGTAGATTTAGGTTTCGGGATAAGTAATTTTA TAAGATTGGAGATTAGAAGTTTTTATTTTTTCGCGTTGCGTTTCGCGTAAT TTTAAATTAAAATTTAGAGATAATGGTTTTCGTCGAGGATATATTTTGAAC GTTAGAATTTTTTTCGATTCGGTCGTGGATACGTTTTTAGTTATTAACGTT GTATTTCGAGTTTGTTGACGCGGAGATATTCGTAGAGTTAGGTTTTGGGTT CGGGACGTTCGGCGGTTGTAAATTCGGTTCGGAGTCGTAGTTTTTAATTT ATAGTATTTTCGAGTTCGTTGGTTGGACGCGGCGGAGGCGTTTCGGGGG CGGATGATGTTTTCGGTAGCGGGTCGCGGTAGAGGTTTAGTATGTAC GGTTATCGTCGTAGTATTCGTTTGGAGTAGGGTTTATTAGGCGTGTAGAAG GAAGGGTAGGTAGTGGGCGTGTA [SEO ID NO: 50]

FIG 1DD

FIG 2A

GTCAGGTGGGCTACTCCACCAGGGAGGCCTTCTCCCCACCCCTGGCCCAGGGCCCTTCCG GATTTCCAGAGAATTCTGGAACCAAGACCTTCCCCTTTCTCACCAGGGACCTCCTTGCTC ${\tt CAGGGCCTCCCGAGCGCCTGGCCGTGAGGCAGGGCCAGAAGGCCAGGGCGGGATCCAGG}$ TGGCTGGCCTCACCCACTGGGACGTGCCCAACCTGGAGACATTGCACCAGGTAGGGCTGC ACCGCTCTCCGAGACCCCGCCCCGTGCTTCCACTTGGGGGCGGGGACCCTGCACCTGACC AGCCCTTCGCCCCGCCTTCCAGATGCTGAAACTGGGGAGGAGCAACCGGGCCACCGCCGC CACCGCCATGAACCAGCGCAGCTCCCGCTCGCATGCCCTGGTCACGCTGACGCTGCGCGC GGCGTCTCCACCGCGCTCCAGGCACCGCAGGTACCACGGCCGGTGCCTGAGCCCTGCG GCACGCTGCACCTGGTGGACCTGGCGGGATCCGAACGCGCACGGAAGGCAGGGGCGGCCG GCCCGCCGCGGGAGACCCAGACGCCCCGGCGCCTGCGGGAGGCCCAGACCATAAACC GCTCGCTGCTGCCGCTAGGAGGCGTGATGCCCGCACTGCGGGCCCACCGGCCGCACGTGC CCTTCCGCGACTCGCAGCTCACGCGACTGCTGCAGCCGGCGCTGGGCCCAGGCACCACCG CCACCGGGCCCGCCCACCGCGCCTCTTGCCCGCAGATCTCCACGCGGCCGGAGGATCT $\tt CGGGGAGACAGTCTGCTCCATCAAGTTCGCCGACCGAGTGGGTCAAGTGGAGCTGGGGCC$ AGCCCGCGCGCAGGGTCCCGCGCTCCTCCGGGACGCCTTCTTCCCTCAGCACCGACAC TCCGCTCACCGGGACCCCCTGCACCCCTACGCCGTCCCCTGGCAGTCCTCCATGCCCCAG TCCCGACAACGGCTCGGGCTCTCGCGCCCGCAGAGGGCCTGCCCCTCTAGTCCTG GGTCGCGGCCCTGCCCATGGGGTCTCAGGCCAGGTCTCTGCTGGCAGAGGCGGTAGTAAA GTCCCTGTACCCCGTCTCCCAGGGCACAAGCTCCCTAGCCTCTTTGGATCCATTGCCCCT GAGCTCCCAGAGTCACCCCTCCACCTCCGCAGCCAGTGAA

[SEQ ID NO: 119] - KIFC2

 ${\tt TTCACTGGCTGCGGAGGTGGAGGGGGAGCTCAGGGGCCAATGGATCCAAAGA}$ GGCTAGGGAGCTTGTGCCCTGGGAGACGGGGTACAGGGACTTTACTACCGCCTCTGCCAG CAGAGACCTGGCCTGAGACCCCATGGGCAGGCCGCGACCCAGGACTAGAGGGGCAGGCC $\tt CTCTGCGGGCGAGAGCCGAGCCGTTGTCGGGACTGGGGCATGGAGGACTGCC$ AGGGGACGCGTAGGGGTGCAGGGGGTCCCGGTGAGCGGAGTGTCGGTGCTGAGGGAAGA AGGCGTCCCGGAGGAGCGCGGGACCCTGCGGCCGGGCTGGCCCCAGCTCCACTTGACC CACTCGGTCGCGAACTTGAGGGAGCAGACTGTCTCCCCGAGATCCTCCGGCCGCGTGGA GATCTGCGGGCAAGAGGCGCGGGTGGGCCGGGTGGGCGGCGACCGCACAC ACCTGCCCGCCCGGCGCCCACCTGCAGCAGCAGCACCGCGGTGGTGCCTGGGCCCAGC GCCGCTGCAGCAGTCGCGTGAGCTGCGAGTCGCGGAAGGGCACGTGCGGCCGGTGGGCC CGCAGTGCGGCCATCACGCCTCCTAGCGCCAGCGAGCGGTTTATGGTCTGGGCCTCC GACATGGGGGAAGGCCGGGCCTCGGGTGCTCTGGAGACTCCGCAGGGCTCAGGCACCGGC CGTGGTACCTGCGGTGCCTGGAGCGCGCGTGGAGACGCCGCGCGCAGCGTCAGCGTGAC ${\tt CAGGGCATGCGAGCGGAGCTGCGCTGGTTCATGGCGGTGGCCGGTTGCT}$ $\verb|CCCCCAAGTGGAAGCACGGGGCGGGTCTCGGAGAGCGGTGCAGCCCTACCTGGTGCAAT| \\$ ${\tt GTCTCCAGGTTGGGCACGTCCCAGTGGGTGAGCCACCTGGATCCCGCCCTGGCCT}$ TCTGGGCCCTGCCTCACGGCCAGGCGCTCGGGAGGCCCTGGAGCAAGGAGGTCCCTGGTG AGAAAGGGGAAGGTCTTGGTTCCAGAATTCTCTGGAAATCCGGAAGGGCCCTGGGCCAGG GGTGGGGAGAAGGCCTCCCTGGTGGAGTAGCCCACCTGAC

[SEQ ID NO: 120] - KIFC2

FIG 2B

CGACCAATGAAACCCCGATACAGAAAATCGCTGTCATGAGTAAGTTAGCACTCCTGAAGA GTTTGAATACTGAACTGGCCAGAGTCTGCGCGCCGACGCCCCCAGGTGGCCGGAGTGAC CCGGAGCAGGCGTGTCTCTCAGACCCGCGCTTGGGCCCGAACAGTTTGTCCCCAC TCCCTGGCGGCTTCTCAAACCAACCCGCCGCTACTGCGCATGCTTGGCAAGCTCGCCCGC ${\tt TCCTTAATATCCTGCTCCGGCTGTTCCTGCCACCCGTTGGTCAAATTCGCACCCAGCTCT}$ GCTCCAGACAGAGGGAAAACCCAGTGATTTCCGGGCTCTAGAAACAAAGGGAGGCTATGA TTCCCTGCTGGCCCTAGGGGTCCAGGGAAGGTTATGGAAAGATAATTCTTTGTGTAAGCG GGTTGCGTAC

[SEQ ID NO: 121] - c20orf23

GTACGCAACCCGCTTACACAAAGAATTATCTTTCCATAACCTTCCCTGGACCCCTAGGGC CAGCAGGGAATCATAGCCTCCCTTTGTTTCTAGAGCCCGGAAATCACTGGGTTTTCCCTC TGTCTGGAGCAGAGCTGGGTGCGAATTTGACCAACGGGTGGCAGGAACAGCCGGAGCAGG CCGCCAGGGAGCCAGCGCGCGACCTAGCTGGCTGGGCCAGGGGAGGGGCCCGCCTTATA TGGGAGCTGCGTGGGGACAAACTGTTCGGGCCCAACGCGCGGGTCTGAGAGACAGCCACG GTATTCAAACTCTTCAGGAGTGCTAACTTACTCATGACAGCGATTTTCTGTATCGGGGTT TCATTGGTCGGTGGTTTAGAAGGTTTTGCTCATTCATTCGTTAATGTAATTCCAACAACC TACACGTGTT

[SEQ ID NO: 122] - c20orf23

CAGCCGAGGGGCGCCTGGCTGATGTGTGTTGAATGGAGAGCGGCCCAACCCTCCTCC TTCCTCCTCTTCTTCCCCGCCCTGACACCCGGGCCTCAAACTTCAACCAAAGCCCGTG AAACTCGGTCTCCCCGAGAGATGAACTTGGACATCAGCAAAGATCCCGAGCACTGCCGGC TGGCTCCTAGACCGGTCTCCCGACCCAGTGTAGACTTCGGTGCCCCGGGCGCCCCCCGGC GTTAATTTACTCTCGAAACAGCCAAAATGGAGGTCAGCTTATAAATTTTCTAAAGCCAGG TCTGGCCGGG

[SEQ ID NO: 123] - GFRA1

 $\tt CCCGGCCAGACCTGGCTTTAGAAAATTTATAAGCTGACCTCCATTTTGGCTGTTTCGAGA$ GTAAATTAACAACAACAAAAAAAGCCTAACATGTACACAGCCCTTCGCCCCAACCCCTGG GACCGCTGGTTCCCAGTCGTGCTCACCCCCCGCCCCCACGCCTGACACACGCTCCC CTTCCCGCACGCCGGGGGCCCCGGGGCACCGAAGTCTACACTGGGTCGGGAGACCGGT CTAGGAGCCAGCCGGCAGTGCTCGGGATCTTTGCTGATGTCCAAGTTCATCTCTCGGGGA GACCGAGTTTGAATCAAATCTGCGTGCGCCCAGCTGTCAAATCTGCAAACCTATCACGCC AGACAATGGGCCGCGCGGAGGACAGACAAGAATGGCTCATTTTGATCGAGGGGGGTAAA TTGAAAAGGGCACGGGCTTTGGTTGAAGTTTGAGGCCCGGGTGTCAGGGCGGGGAGAAGA AGAGGAGGAGGAGGGTTGGGCCGCTCTCCATTCAACCACACATCAGCCAGGCGCGC CCCTCGGCTG

[SEQ ID NO: 124] - GFRA1

FIG 2C

AGAAACTGAGGTCGGAGTGGGGGCGTGACCAGGCCAGCCTAAGGCCGCTGCACTAATGAG AAGCTGAGCTCTCAGATTTTTGCCTCCCTGTCCCTGCCAAGTCGCTGTTTCCTGGGACAA GAGGGAGCCTCACTGAAACGAACTCCGGTCTCAGGGGACAGAATCCTGAAACCCTGGCTC TGGGGTCCGGGGCAGGGTGCGCTGCCTCAGGACAGACGGTGAAACTGAGGTCCAGAGCC GGACATCCACCGCCTGCGGAGGGAACGAGAACGCGGCGCGTCCTGCCTTGCGGGCCGAGC GGCGCCAGAGCCGCCTCCTCCCGCCCCCGCGCTAGATCCCCCGCCCCGTCTTTGCCCT GCTCCTGTGGGCTGCGGCCTGCGCGCAGCAGGAGCAGGACTTCTACGACTTCAAGGCGGT CAACATCCGGGGCAAACTGGTGTCGCTGGAGAAGTACCGCGGATCGGTGAGTGCGCGGGG TCTGGCGGCGCCTGGGCCTCGCCCTGGCGGGGCCTGCTGGGGACGCCCGCAG CCCGGTCCCCGCGCGCGTGTGGCTCCGAGGACGCTCCAGCCGCGGCCGCCAAACCCCG GCCCCGCCCGCTCGGCCGTGACCTCTGGCGCGCGCCCCCATCCCGCGCCCGGCCCGG CCCGGCCCGCGCTACGTGGCACGGCCTTGGCGCGGAGGAACCCGAAGCGCTCGCAGTCG GCGCCCACTTCGCTACCGGCACCTTTGGGCAGCGGGGTCCAGACCTTCGCCGGGAGGCCG GGCACCACTGCCCAGCCTTTGCCATTCACGGGTGAAAAAAGTAACCGTAGCATCGTGCGG $\verb|CCTTTCCCTCTCCCGTCCTCATTTTCTGCATCTGGAACGGGGAGTGGCTGATTCGGAGTC| \\$ GGAGACCTCACACGGATCATCCCTGGGAGA

[SEQ ID NO: 125] - GPX7

GCACATTGATCTCCACAGTGTTCTTCACTGGACTCCGGAATCAGCCACTCCCCGTTCCAGA TGCAGAAAATGAGGACGGGAGAGGGAAAGGCCGCACGATGCTACGGTTACTTTTTTCACC CGTGAATGGCAAAGGCTGGGCAGTGGTGCCCGGCCTCCCGGCGAAGGTCTGGACCCCGCT GCCCAAAGGTGCCGGTAGCGAAGTGGGCGCCGACTGCGAGCGCTTCGGGTTCCTCCGCGC CCTCGGAGCCACACCGCGGGGGGACCGGGCTGCGGGGGCGTCCCCAGCAGGCCCCGCCAG GGCGAGGCCGGGCCAGCGGCGCCAGACCCCGCGCACTCACCGATCCGCGGTACTTC ${\tt TCCAGCGACACCAGTTTGCCCCGGATGTTGACCGCCTTGAAGTCGTAGAAGTCCTGCTCC}$ TGCTGCGCGCAGGCCGCACAGGAGCCACGCCGCTGCCACCGTCGCCACC ATGGCTTGTTCCGGAGGTGGCGCGTCGCGAGGGCAAAGACGGGGCGGGGGGATCTAGCG CGGGGGGGGGGGGGGCGCTCTGGCGCCGCTCGGCCCGCAAGGCAGGACGCCCGCGT ${\tt TCTCGTTCCCTCGCAGGCGGTGGATGTCCGGCTCTGGACCTCAGTTTCACCGTCTGTCC}$ TGAGGCAGCGCACCCTGCCCGGACCCCAGAGCCAGGGTTTCAGGATTCTGTCCCCTGA GACCGGAGTTCGTTTCAGTGAGGCTCCCTCTTGTCCCAGGAAACAGCGACTTGGCAGGGA ${\sf CAGGGAGGCAAAAATCTGAGAGCTCAGCTTCTCATTAGTGCAGCGGCCTTAGGCTGGCCT}$ GGTCACGCCCCACTCCGACCTCAGTTTCT

[SEQ ID NO: 126] - GPX7

TTCTCTTACGATCTGGCTTTACTCTCACGCGCACAGCCGAGTCCCTGGGGGACCCAGCAGA GGTCCGAAGCGGAGCGGGGGGGGGGCTACGGAAGCTGGCGAGGCCGAGCCCCTCCT ${\tt AGTGCTTCCGGACCTTGCTCCCTGAACACTCGGAGGTGGCGGTGGATCTTACTCCTTCCA}$ AGGGGGGGGTCTGGCGTAGGTCCAGCCCCTGCGTGCCGGGAACCCCAGAGGAGGTCGC ACTGGGGTACTGGGACATCCGCGGGGTGAGTGAGGGTCCGCTGCACTGTGGGACCGGGCG CGTGGGCGGAAGTGCCGAGCGGCTGGGGACCGGCTCTAGGGACGGTTCCCTCCTTAGGG CTATCTCTCA

[SEQ ID NO: 127] - GSTM4

FIG 2D

TGAGAGATAGCCCTAAGGAGGGAACCGTCCCTAGAGCCGGTCCCCAGCCGCTCGGCACTT GTACCCCAGTGTCATGGACATGATGCTGGTTGGTGTCGATTCTGCAGACAGGCCTCAGCT GGGCTGAACTGCGACCTCCTCTGGGGTTCCCGGCACGCAGGGGCTGGACCTAGCGCCAGA CCCGCCCCTCGGCCCGCTGCGCCCGCCGATCTTCAAGGTCGTCACTTCCAACCGGCCG ATCTTCAAGGTCGTCACTTCCAACCAACAGGCGCGGGAGCACGGAGCAGGTTGCTGGAT $\verb|CCTCACTGGCTGGAAGGAGTAAGATCCACCGCCACCTCCGAGTGTTCAGGGAGCAAGGTC|\\$ CGGAAGCACTAGGAGGGCTCGGCCTCGCCAGCTTCCGTAGCCCCGCCCCGCCCCGCTCC GCTTCGGACCTCTGCTGGGTCCCCAGGGACTCGGCTGTGCGCGTGAGAGTAAAGCCAGAT CGTAAGAGAA

[SEQ ID NO: 128] - GSTM4

TCTTGAATTGGGGGCGGAGGTAAAAAAAAAAAAAAGTCCTCACTGTGGGAAGCTATAAA AAGCAAAGAGGACTGGGGAGAGAGAGAGAGAGAGAAAGCGGGAGCCCGCGGCGAGCGTA GCGCAAGTCCGCTCCCTAGGCATCGCTGCGCTGGCAGCGATTCGCTGTCTCTTGTGAGTC AGGGGACAACGCTTCGGGGCAACTGTGAGTGCGCGTGTGGGGGACCTCGATTCTCTTCAG ATCTCGAGGATTCGGTCCGGGGACGTCTCCTGATCCCCTACTAAAGCGCCTGCTAACTTT AAAAGCAACTGAGTTGAAGGAGAAGGAGCTGATGCGGGCCTCCTGATCAATTAAGAGGAG AGTTAAACCGCCGAGATCCCGGCGGGACCAAGGAGGTGCGGGGCAAGAAGGAACGGAAGC GGTGCGATCCACAGGGCTGGGTTTTCTTGCACCTTGGGTCACGCCTCCTTGGCGAGAAAG CGCCTCGCAT

[SEQ ID NO: 129] - DKK2

ATGCGAGGCGCTTTCTCGCCAAGGAGGCGTGACCCAAGGTGCAAGAAAACCCAGCCCTGT GGATCGCACCGCTTCCGTTCCTTCTTGCCCCGCACCTCCTTGGTCCCGCCGGGATCTCGG CGGTTTAACTCTCCTCTTAATTGATCAGGAGGCCCGCATCAGCTCCTTCTCCTTCAACTC AGTTGCTTTTCTCCTCTTTTTCCTATCCTTTATGTGTCAAACTTTGCAGGACACAGT GCTCCTTTTCAAAGTTAGCAGGCGCTTTAGTAGGGGGATCAGGAGACGTCCCCGGACCGAA TCCTCGAGATCTGAAGAGAATCGAGGTCCCCCACACGCGCACTCACAGTTGCCCCGAAGC GTTGTCCCCTGACTCACAAGAGACAGCGAATCGCTGCCAGCGCAGCGATGCCTAGGGAGC CAATTCAAGA

[SEQ ID NO: 130] - DKK2

CGATTGGCTGCAAGGGTCTCGGCTTGGCCGCGGATTGGTCACACCCGAGGGCTTGAAAGG TGGCTGGGAGCGCCGGACACCTCAGACGGACGGTGGCCAGGGATCAGGCAGCGGCTCAGG CGACCCTGAGTGTGCCCCCACCCCGCCATGGCCCGGCTGCTGCAGGCGTCCTGCCTT TCCCTGCTCCTGGCCGGCTTCGTCTCGCAGAGCCGGGGACAAGAGAAGTCGAAGGTGAGT GAGCCTCCGGGCCGGGGCCGGGAGAAAAAACCTAGCCCCTCGGTGTCCAGCGCTCAGTG CAATGCACCCTTTTCCCAGGCTCCCGCCAGATGGGCAATCCCCAGGTGCGAGAGACCT $\verb|CCTGAACCCCTTTTGCCGCCCCCTCCGCCGGGGACCCCGGCCCCGACCGTCGTCTT| \\$ CGTAGTTCCATCTGTTGGAGAGCCGAGACCTGGTGCTTCAGGCGGGCAGAATGACTAAGG GAGGAAGGTCTCTCCCCGAGCTCGCACTTTCTCCCCACTGCCACCTCGAGGGTCGCCT TGCTACATCT

[SEQ ID NO: 131] - GPX3

FIG 2E

AGATGTAGCAAGGCGACCCTCGAGGTGGCAGTGGGGAGAAAGTGCGAGCTCGGGGAGAGA GACCTTCCTCCCTTAGTCATTCTGCCCGCCTGAAGCACCAGGTCTCGGCTCTCCAACAGA GGGGTTCAGGAGGTCTCTCGCACCTGGGGATTGCCCATCTGGCGGGGAGCCTGGGAAAAG GGGTGCATTGCACTGAGCGCTGGACACCGAGGGGCTAGGTTTTTTCTCCCGGCCCCCGGC CCGGAGGCTCACCTCCACCTTCTCTCTTGTCCCCGGCTCTGCGAGACGAAGCCGGCCA GGAGCAGGGAAAGCAGGCAGGACGCCTGCAGCAGCCGGGCCATGGCGGGGTGGGGGCACA CTCCCAGCCACCTTTCAAGCCCTCGGGTGTGACCAATCCGCGGCCAAGCCGAGACCCTTG CAGCCAATCG

[SEQ ID NO: 132] - GPX3

AGGGGAACTGGTATCTCCACAGTAATTACTAGAGCAGCTCTGGGGAACGGAGGGTTGGCT AAGGAAGAAAAGCTCCCCCAACCCTTGGGGCGAGGGAGCGTTCTCTCAATGGAGCCCCCC CAACTCCCCTCCACCCCCACCAGTCTTCCAGGAAAGAGGAATACCCTACCCGGCAGGGC TGCGAAGGAAGGGAAATCCAACCAGAGCGAAAGTCGCACGCGGACAGCTCTGCCAGCCC TTGGAGGCATCCGGCGGTCACCCACGGGACAAAGCGCGGCTGCGGGAGCGCGCGGGGC ATTCCGGACCCGCGTCGAGCTCCGCTCTAGAGGGGGCGGCGGCGGCGACAAGCCGGAGA GAGGAAGGGCCAAGGAGCACGCCCTCCTGTCGGCACCATCAGCGGGAGAGTGGCGAGCG GACGCCTAGACGGAGGGCCCTACTCAGACCCCATCGAGCCAGTTCCCAAGCTTTTCCCT $\verb|CCGACCTGCTCCCTGCGGGGCGCGTGAGGGTGCGGGGTCGGGGGTGAACCTGGTGTTGGG| \\$ GAAAGTGATT

[SEQ ID NO: 133] - RASSF5

AATCACTTTCCCCAACACCAGGTTCACCCCCGACCCGCACCCTCACGCGCCCCGGGAGGG AGCAGGTCGGAGGGAAAAGCTTGGGAACTGGCTCGATGGGGTCTGAGTAGGGCCCCTCCG TCTAGGCGTCCGCTCTCCCGCTGATGGTGCCGACAGGAGGGCCGTGCTCCTTG GCCCTTCCTCTCCGGCTTGTCGCCGCCGCCGCCCCTCTAGAGCGGAGCTCGACGCG GGTCCGGAATGCCCCGCGCGCGCTCCCGCAGCCGCGCTTTGTCCCGTGGGTGACCGCCGG $\tt ATGCCTCCAAGGGCTGGCAGAGCTGTCCGCGTGCGACTTTCGCTCTGGTTGGATTTCCCC$ TTCCTTCGCAGCCCTGCCGGGTAGGGTATTCCTCTTTCCTGGAAGACTGGTGGGGGGTGG AGGGGAGTTGGGGGGGCTCCATTGAGAGAACGCTCCCTCGCCCCAAGGGTTGGGGGAGCT TTTCTTCCTTAGCCAACCCTCCGTTCCCCAGAGCTGCTCTAGTAATTACTGTGGAGATAC CAGTTCCCCT

[SEQ ID NO: 134] - RASSF5

FIG 2F

CGGGCAAAAATGGAGAGCAGGCAGAGGTCACATCCTCCTCTTCCTCACGCTCCCGGG $\tt CTGCGTGCCCACAGGGGCACAGCCCTGTGCGCGGTGCCACCGGGGGCCATCAGGCTGGGT$ ${\tt CCGGGAGGGAGAAGTGGCCCCCTTCCCCCGCCCGCGCGCTCCCCCGGGCGTGAGGCTCT}$ CCGGGCGGCGGGGCGGGCGAGGCTGACAGTCCCCGGCGGCCCCTCCTCCCCCACGG GGTGCGCCTGGCCCGGCCCAGCCCCTCTCCGGGGTTTCCCCGGGTGCTCTCCTCGCT TTCTCTTTGTCTCTGCTGTTCTTCTCGGGCTCCCGGGTTCCCACCCGCCTGTGCTCTCC CCCGCCCCGCGCTCCCCTCCGCCCTCACTCCCAGCGCGAGTGGCGGCGGCGGCGGAGC GCGCCGCCCCCGCGCATGGAGCTGGCAAGCCCGCCTGAGGCGGGACGCCCTGCTA GACGCGATCGGGGGCATCTGAGAGGGGACCCCGGGCTGCGAGACGAAGGGGCGCGGGCCG TGCAGAGTCGGGGTCCCCCAGCTCTCCTGCGCCCGAAACTTGGGGTGCGAGGGGGGCTGG TCGCGGACGGGGAGACCGCTCAGGCATGCCCCTCGGGCGGCGTGGGGGCGGCGGTGGCG $\tt GGGAAGCAGAGCGTTCTCCCGCCGGGCGGGAAGAAGGGGCGCGAGCGGTGCGGACTTGG$ AGGGCCCGGGCTTCGCCGCCGCGGGACTTTGGGGGAGAGAGGCGGGCAGTCGGCTGCGG GGTGGGTGCCCAGGAAGCCGGGCGTTCTCCCGCATCTCCGCTCGCCACCCCGCCGAGAGC TGGAGGGCGCGGGCTGCCTGAGCGCAGCTCCCTTCTCTCCCCAGGCGCCCTTCTGC CGCAGTGTGGGAGGCGCTGGCGGCGCTGGCGGTGCCTGGTGGGCGCGGTGCG CGGCGGGCCCGGGCTCAGCATGTTCGCGGGCCAGGCGCGCAGCCCGATCCCTGCTCGGA CGAGAACGGCCACCCGCCGCTGCATCCCGGACTTTGTCAATGCGGCCTTCGGCAAGGA CGGCGAGGAGCGCTGCGCTCTGCCACCTCTGCAACGCGTCCGACCCCAAGAAGGCGCA $\tt CCCGCCCGCCTTCCTCACCGACCTCAACAACCCGCACAACCTGACGTGCTGGCAGTCCGA$ GAACTACCTGCAGTTCCCGCACAACGTCACGCTCACACTGTCCCTCGGCAAGAAGTTCGA AGTGACCTACGTGAGCCTGCAGTTCTGCTCGCCGGGCCCGAGTCCATGGCCATCTACAA GTCCATGGACTACGGGCGCACGTGGGTGCCCTTCCAGTTCTACTCCACGCAGTGCCGCAA GATGTACAACCGGCCGCACCGCGCCCCATCACCAAGCAGAACGAGCAGGAGGCCGTGTG CACCGACTCGCACACCGACATGCGCCCGCTCTCGGGCCGCCTCATCGCCTTCAGCACGCT GGACGGCCGCCCTCGGCGCACGACTTCGACAACTCGCCCGTGCTGCAGGACTGGGTCAC GGCCACAGACATCCGCGTGGCCTTCAGCCGCCTGCACACGTTCGGCGACGAGAACGAGGA CGACTCGGAGCTGGCGCGACTCGTACTTCTACGCGGTGTCCGACCTGCAGGTGGGCGG CCGGTGCAAGTGCAACGGCCACGCGGCCCGCTGCGTGCGCGACCGCGACGACAGCCTGGT GTGCGACTGCAGGCACAACACGGCCGGCCCGGAGTGCGACCGCTGCAAGCCCTTCCACTA CGACCGCCCTGGCAGCGCCCACAGCCCGCGAAGCCAACGAGTGCGTGGGTGAGTGGGG GCGAGTTCATAGGAGCGCGGGTCGAGGGAACGGCGGAGGCGCGTTCGCCGATGCCCGGG ACCCGGGAGGGCTCAGAGCAGGTCCACTCGCTCGCGTGGCGCTCGTGGTGGACGCCCGAA TTTGCGCCCAGTGCTCTCTGCGAAGCCAAGAAGCAGCAGGAGAAATGTTCCCGGGAGGGG GTTTGCAGAACATTTGCAGATAGGTCTCCGCTAACCCTGGATCCAAACGCAAACATTCA TTGCCTTCCCCCTCGTTGGGTTGGACGCTGGGATTCACCT

[SEQ ID NO: 135] - NTN1

FIG 2G

CAGGGTTAGCGGAGACCTATCTGCAAATGTTCTGCCAAACCCCCTCCCGGGAACATTTCT CCTGCTGCTTCTTGGCTTCGCAGAGAGCACTGGGCGCAAATTCGGGCGTCCACCACGAGC GCCACGCGAGCGAGTGGACCTGCTCTGAGCCCTCCCGGGTCCCGGGCATCGGCGAACGCG $\tt CCTCCCGCCGTTCCCTCGACCCGCGCTCCTATGAACTCGCCGCTGCGAGGCCCAGCAGCT$ CCCGCCGGGGCCCACCGGCGCGCGCGCGCGCGCACCCACTCACCCACGCACTC GTTGGCTTCGCGGGCTGTGGCGCCTGCCAGGGCCGGTCGTAGTGGAAGGGCTTGCAGCG GTCGCACTCCGGGCCGGCCGTGTTGTGCCTGCAGTCGCACACCAGGCTGTCGTCGCGGTC GCGCACGCAGCGGGCCGTGGCCGTTGCACTTGCACCGGCCGCCCACCTGCAGGTCGGA CACCGCGTAGAAGTACGAGTCGCGCGCCAGCTCCGAGTCGTCCTCGTTCTCGTCGCCGAA ${\tt CGTGTGCAGGCGGCTGAAGGCCACGCGGATGTCTGTGGCCGTGACCCAGTCCTGCAGCAC}$ GGGCGAGTTGTCGAAGTCGTGCGCCGAGGGCCGCCCGTCCAGCGTGCTGAAGGCGATGAG ${\tt GCCGCCGAGAGCGGCGCATGTCGGTGTGCGAGTCGGTGCACACGGCCTCCTGCTCGTT}$ $\tt CTGCTTGGTGATGGGCGCGGTTGCGGCCGGTTGTACATCTTGCGGCACTGCGTGGAGTA$ GAACTGGAAGGGCACCCACGTGCGCCCGTAGTCCATGGACTTGTAGATGGCCATGGACTC GGGCCGCGGCGAGCAACTGCAGGCTCACGTAGGTCACTTCGAACTTCTTGCCGAGGGA CAGTGTGAGCGTGACGTTGTGCGGGAACTGCAGGTAGTTCTCGGACTGCCAGCACGTCAG $\tt GCGCGCGGGGGCCGCAGGTGCTGGACACGCGCACGTCCTTGCCGAAGGCCGCATT$ GACAAAGTCCGGGATGCAGCGGCGGGTGGCCGTTCTCGTCCGAGCAGGGATCGGGCTG CGCCGCCTGGCCCGCAACATGCTGAGCCCGGGCCCGCCGCACCGCGCCCACCAGGCA CGCCACCGCCGCCAGCGCCAGCGCCTCCCACACTGCGCGCATCATGCTGCGTCCAGC TTGCCCCGGCCCTGCCGCGGAGATCTGTCCGCCTGCCGCAGAAGGCGCCTGCGGAGA GAAGGGAGCTGCGCTCAGCCAGCCCGCCCCTCCAGCTCTCGGCGGGGTGGCGAG CTCTCCCCCAAAGTCCCGCGGGCGGCGAAGCCGGGGCCCTCCAAGTCCGCACCGCTCGCG $\tt CCCCTTCTTCCCCGCCGGGGGGGGGGGGGGGGGCTCTGCTTCCCCGCCACGCCGCCCCCCACGC$ ${\tt CGCCCGAGGGGCATGCCTGAGCCGGTCTCCCCGTCCGCACCAGCCCCCTCGCACCCCA}$ CGCAGCCCGGGGTCCCTCTCAGATGCCCCCCGATCGCGTCCCCGCCGGAAAGTCCGCGTT CGGGACTTTACCTCTGGAGGGGGCAAAAGAAAGAAAAGTTTGCCTGGCCCCTCCGGGG AGCCCGCGCCGGTCGCCGGAGAGCCTCTCGCTCGCTAGCAGGCGCGTCCCGCCTC AGCGCGGGCTTGCCAGCTCCATGCCCGGCGGCGCCGCTGCCCCAGCCCCAGCCCCGG TCCCGGCCCGCCGCCTCTCTCGCCCGAGTGACTACGCGGCCGCCCGGCTCCCGCCG GCCGGCGCACTCACACACGCGCGCTCGCCCCGAAGGCTCCGCCGCCGCCGCCACT GCGCCGGCCAATAACGTCCGCGAGCTGCCGCCAGCTCCGAGCAAAGTTTTCACCCCGGGA AAGAAGAAAGTTAAAGGGAACCGGCCCGGACGCCCGAGAGGGAGACCACAGGCGGGTGGG AAACCCCGGAGAGGGGGTGGGCCGGGCCAGGCGCACCCCGTGGGGGAGGAGGGCCG $\tt CCGGGGACTGTCAGCCTCGCCCGCGCCCCGCGCCCGGAGAGCCTCACGCCCGGGGGA$ GCGCGCGGGCGGGGAAGGGGGCCACTTTCTCCCTCCCGGTCCCAGCCAAACACATCTGT GTTTGTTTTCTTTGCTGCGCGGAGGTCGGGCCTTCCTCTAACCCAGCCTGATGGCCCCCG GTGGCACCGCGCACAGGGCTGTGCCCCTGTGGGCACGCAGCCCGGGAGCGTGAGGAAGAG GAGGAGGATGTGACCTCTGCCTGCTCTCCATTTTTGCCCG

[SEQ ID NO: 136] - NTN1

FIG 2H

GCAGTCCTGTGTGACTGGTGAGACTCTTGTAGGGGGCGTTTCTACAACGACGAAACCCTTC CTAGGCACTCACTCCAACAGAATAACAAGCCCATTTTATTAGTATTTCGTTTTCCATGTA AAGTTCTGCTCATACGAATATATTTATAATTCTGATTTTTTTACGGCATTGGGGAGCACA CCGACAGGCTGCTGAACGGTGGCTGGAGATTCGAGGGAAAACGAAGTTCGCCGAGGCGGC $\tt CTCGGGCGGCAGGTCCCGGGCTCCATCACAGGGCACACGCGGCTACCAGGGACGCAGCC$ CTCATGCCTGGCAACCCAGCAGAAACTTCGGACTGGGGCAAAACAAGCCCGGGCCCCGGC GGCACGCGGGCTAGGCGCGTTCCCGCCAGTACCTGGTCGCGAGGCCGCTCGCGGGGTGC GGAGGGGGCGCAGCAGATTCCCTTCCAGCAAGCGCGTGAGGGGCATTCTCAACGCAAA ACCAGACCCAGAAAGTAGTGACCAGCCCTCCTCGGATTACCCTTCATTGGCTCCTCCCTT GCTCCCCCACCCTCCAGATTTGCATAAAAAAGGCCAAGAAAACTCTGGCTGTGCCCCAG CAACGCTCATTCTGCTCCCCGGGTCGGAGCCCCCGGAGCTGCGCGCGGGCTTGCAGC GCCTCGCCCGCGCTGTCCTCCCGGTGTCCCGCTTCTCCGCGCCCCAGCCGCCGGCTGCCA GCTTTTCGGGGCCCCGAGTCGCACCCAGCGAAGAGGCGGGCCCGGGACAAGCTCGAACT $\tt CCGGCCGCCTCGCCCTTCCCGGGCTCCGCTCCTCTGCCCCCTCGGGGTCGCGCCCAC$ GATGCTGCAGGGCCCTGCTGCTGCTGCTCTTCCTCGCCTCGCACTGCTGCCTGGG CTCGGCGCGGGCTCTTCCTCTTTGGCCAGCCCGACTTCTCCTACAAGCGCAGCAATTG CAAGCCCATCCCTGCCAACCTGCAGCTGTGCCACGGCATCGAATACCAGAACATGCGGCT GCCCAACCTGCTGGGCCACGAGACCATGAAGGAGGTGCTGGAGCAGGCCGGCGCTTGGAT CCCGCTGGTCATGAAGCAGTGCCACCCGGACACCAAGAAG

[SEQ ID NO: 137] - SFRP2

CTTCTTGGTGTCCGGGTGGCACTGCTTCATGACCAGCGGGATCCAAGCGCCGGCCTGCTC CAGCACCTCCTTCATGGTCTCGTGGCCCAGCAGGTTGGGCAGCCGCATGTTCTGGTATTC GATGCCGTGCACGCTGCAGGTTGGCAGGGATGGGCTTGCAATTGCTGCGCTTGTAGGA GAGGAAGAGCAGCAGCGAGCCAGGGCCCTGCAGCATCGTGGGCGCGCGACCCCGAGG GGGCAGAGGGAGCCGGGGAAGGGCGAGGCGGAGTTCGAGCTTGTCCCGGGC $\tt CCGCTCTTCGCTGGGTGCGACTCGGGGGCCCCGAAAAGCTGGCAGCCGGCGGCTGGGGC$ GCGGAGAAGCGGGACACCGGGAGGACAGCGCGGGGCGAGGCGCTGCAAGCCCGCGCGCAGC ${\tt TCCGGGGGGCTCCGACCCGGGGGAGCAGAATGAGCCGTTGCTGGGGCACAGCCAGAGTTT}$ TCTTGGCCTTTTTTATGCAAATCTGGAGGGTGGGGGGGGAGCAAGGGAGGCCAATGAAGG GTAATCCGAGGAGGCTGGTCACTACTTTCTGGGTCTGGTTTTGCGTTGAGAATGCCCCT $\tt CACGCGCTTGCTGGAAGGGAATTCTGGCTGCGCCCCTCCCCTAGATGCCGCCGCTCGCC$ CGCCCTAGGATTTCTTTAAACAACAAACAGAGAAGCCTGGCCGCTGCGCCCCCACAGTGA GCGAGCAGGGCGCGGGCTGCGGGAGTGGGGGGCACGCAGGGCACCCCGCGAGCGGCCTCG CGACCAGGTACTGGCGGGAACGCGCCTAGCCCCGCGTGCCGCGGGGCCCGGGCTTGTTT CGTGTGCCCTGTGATGGAGCCCGGGACCTGCCCGCCGAGGCCGCCTCGGCGAACTTCGT TTTCCCTCGAATCTCCAGCCACCGTTCAGCAGCCTGTCGGTGTGCTCCCCAATGCCGTAA AAAAATCAGAATTATAAATATATTCGTATGAGCAGAACTTTACATGGAAAACGAAATACT AATAAAATGGGCTTGTTATTCTGTTGGAGTGAGTGCCTAGGAAGGGTTTCGTCGTTGTAG AAACGCCCCTACAAGAGTCTCACCAGTCACACAGGACTGC

[SEQ ID NO: 138] - SFRP2

FIG 2I

GCTGCCTTTGTTCTTTGACTACTCAGCCAATTCAGGTCTGAGCTGTTCTTCGACGCCGCC $\tt CTAGATGCGATGATGAAGGTCAGGTGCCCGCATCCCACCGTCCCCTCGCAGGGGCC$ ACCCTTTCCGCGAGAAGCTGACCCTGCGGAAGGCGCTCGTCACCATCGCCGTCATCTGGG CCCTGGCGCTGCTCATCATGTGTCCCTCGGCCGTCACGCTGACCGTCACCCGTGAGGAGC ACCACTTCATGGTGGACGCCCGCAACCGCTCCTACCCGCTCTACTCCTGCTGGGAGGCCT GGCCCGAGAAGGGCATGCGCAGGGTCTACACCACTGTGCTCTTCTCGCACATCTACCTGG ${\tt CGCCGCTGGCGCTCATCGTGGTCATGTACGCCCGCATCGCGCGCAAGCTCTGCCAGGCCC}$ CGGGCCCGGCCCCGGGGGCGAGGAGGCTGCGGACCCGCGAGCATCGCGGCGCAGAGCGC GCGTGGTGCACATGCTGGTCATGGTGGCGCTGTTCTTCACGCTGTCCTGGCTGCCGCTCT $\tt CCGTCTACGCCTTCCCCTTCGCGCACTGGCTGGCCTTCTTCAACAGCAGCGCCCAACCCCA$ TCATCTACGGCTACTTCAACGAGAACTTCCGCCGCGGCTTCCAGGCCGCCTTCCGCGCCC GCCTCTGCCCGCGCCGTCGGGGAGCCACAAGGAGGCCTACTCCGAGCGGCCCGGCGGGC TTCTGCACAGGCGGTCTTCGTGGTGGTGCGGCCCAGCGACTCCGGGCTGCCCTCTGAGT CGGGCCTAGCAGTGGGGCCCCCAGGCCCGCCTCCCGCTGCGGAATGGGCGGGTGG CTCACCACGGCTTGCCCAGGGAAGGGCCTGGCTGCTCCCACCTGCCCCTCACCATTCCAG CCTGGGATATCTGA

[SEQ ID NO: 139] - GPR147

TCAGATATCCCAGGCTGGAATGGTGAGGGGCAGGTGGGAGCAGCCAGGCCCTTCCCTGGG CAAGCCGTGGTGAGCCACCCGCCCATTCCGCAGCGGAGGCGGCCCGGGCCTGGGGGCCCC ACTGCTAGGGCCCGACTCAGAGGGCAGCCCGGAGTCGCTGGGCCGCACCACCACGAAGAC CCGCCTGTGCAGAAGCCCGCCGGGCCGCTCGGAGTAGGCCTCCTTGTGGCTCCCCGACGG GCGCGGCAGAGGCGGCGGAAGGCGGCCTGGAAGCCGCGGCGAAGTTCTCGTTGAA GAAGGCGTAGACGGTGACCAGGTGCAGCTGCGGCGCGCTGAGCTGCCCGTAGTCGATGAG CAGCAGCAGCGCCCAGAGCGGCAGCCAGGACAGCGTGAAGAACAGCGCCACCATGACCAG CATGTGCACCACGCGCGCTCTGCGCCGCGATGCTCGCGGGGTCCGCAGCCTCCTCGCCCCC GGGGGCCGGGCCTGGCAGAGCTTGCGCGCGATGCGGGCGTACATGACCACGAT GAGCGCCAGCGGCCAGGTAGATGTGCGAGAAGAGCACAGTGGTGTAGACCCTGCGCAT GCCCTTCTCGGGCCAGGCCTCCCAGCAGGAGTAGAGCGGGTAGGAGCGGTTGCGGGCGTC CACCATGAAGTGGTGCTCCTCACGGGTGACGGTCAGCGTGACGGCCGAGGGACACATGAT GAGCAGCCCAGGGCCCAGATGACGGCGATGGTGACGAGCCCTTCCGCAGGGTCAGCTT CTCGCGGAAAGGGTGCACGATGCAGCGGAACCTGCCGCGGGGAGAGACAGGCGGGATC ATCATCGCATCTAGGGCGCGTCGAAGAACAGCTCAGACCTGAATTGGCTGAGTAGTCAA AGAACAAAGGCAGC

[SEQ ID NO: 140] - GPR147

FIG 2J

AGAAAGGTAATATTTGGAGGCCTCCGAGGGACGGGCAGGGGAAAGAGGGATCCTCTGACC CAGCGGGGGCTGGGAGGATGGCTGTTTTTGTTTTTTCCCACCTAGCCTCGGAATCGCGGA CTGCGCCCAGTGACGGACTCAAACTTACCCTTCCCTCTGACCCCGCCGTAGGATGACGCC TCAACCCTCGGGTGCGCCCACTGTCCAAGTGACCCGTGAGACGGAGCGGTCCTTCCCCAG AGCCTCGGAAGACGAAGTGACCTGCCCCACGTCCGCCCCGCCCACCCCACTCGCACACG GGGGAACTGCGCAGAGGCGGAAGAGGGAGGCTGCCGAGGGCCCCGAGGAAGCTCCGGGC TCGGCGAAAGAAGGCCAACGACCGCGAGCGCAATCGAATGCACAACCTCAACTCGGCACT GGACGCCTGCGCGGTGTCCTGCCCACCTTCCCAGACGACGCGAAGCTCACCAAGATCGA GACGCTGCGCTTCGCCCACAACTACATCTGGGCGCTGACTCAAACGCTGCGCATAGCGGA CCACAGCTTGTACGCGCTGGAGCCGCCGCGCGCACTGCGGGGAGCTGGGCAGCCCAGG CGGTTCCCCGGGGACTGGGGGTCCCTCTACTCCCCAGTCTCCCAGGCTGGCAGCCTGAG TCCCGCCGCGTCGCTGGAGGAGCGACCCGGGCTGCTGGGGGGCCACCTTTTCCGCCTGCTT GAGCCCAGGCAGTCTGGCTT

[SEQ ID NO: 141] - NEUROG3

AAGCCAGACTGCCTGGGCTCAAGCAGGCGGAAAAGGTGGCCCCCAGCAGCCCGGGTCGCT CCCAGTCCCGGGGGAACCGCCTGGGCTGCCCAGCTCCCCGCAGTGCGGCGGCGGCGGCT CCAGCGCGTACAAGCTGTGGTCCGCTATGCGCAGCGTTTGAGTCAGCGCCCAGATGTAGT TGTGGGCGAAGCGCAGCGTCTCGATCTTGGTGAGCTTCGCGTCGTCTGGGAAGGTGGGCA GGACACCGCGCAGGGCGTCCAGTGCCGAGTTGAGGTTGTGCATTCGATTGCGCTCGCGGT CGTTGGCCTTCTTTCGCCGACTCCGTCGCTGCTTGCTCAGTGCCAACTCGCTCTTAGGCC TCACTTCGTCTTCCGAGGCTCTGGGGAAGGACCGCTCCGTCTCACGGGTCACTTGGACAG TGGGCGCACCCGAGGGTTGAGGCGTCATCCTACGGCGGGGTCAGAGGGAAGGGTAAGTTT CATCCTCCCAGCCCCCGCTGGGTCAGAGGATCCCTCTTTCCCCTGCCCGTCCCTCGGAGG CCTCCAAATATTACCTTTCT

[SEQ ID NO: 142] - NEUROG3

FIG 2K

TTCCTTCTGCACGCCTGGTGGGCCCTACTCCAGGCGGGTGCTGCGACGGTGGCCACTGCG CTCCTGCGTACGCGGGGGCAGCCCTCGTCGCCATCCCCTCTGGCGTACATGCTGAGCCTC TACCGCGACCCGCTGCCGAGGGCAGACATCATCCGCAGCCTACAGGCAGAAGGTAGGCAG ACTCGGGAAGTGCTGTGGGTTGGGGGCTGCGGCTCCGAGCCGGGTTTGCAGCCGCCCGGG CGTTGGTGGCTGGGGGCGTATCCACGGCCGAGTCGGGAAGGGATTCTAGCGTTCAGGGTG TGTCCTCGACGGGGACCATTGTCTCTGGGTTTTGGTTTGGGATTGCGCGGAGCGCAGCGC GGAAGGGTGGGAGCTTCTAATCTCCAGTCTTGTGAAGTTGCTTATCCCGGAGCCTGGGTC TGCGCATCTGTAGGATAGGTGTAATAAATAACACCTCGCCTATCAGACTGTGGAAAGCGC GAGATGACAATGCGCGCAAACGCTCAGCGCAGTTACCCGGCACAGCCACAGTCAACGGTC GAATGGGTCCCGGGGTGTGACGTCGGGAGTATCGGCAGCTGAGCTGGTAACATCGGGGAT TTGGGTCCTCCAGCCGCGCGGGAAGTGTCAAGTGTCTCGCTTAACCCCGGGTTCGGGG CCATGATTTGCAGGGGAGTGGGTGTCAAGGACGGCAGGGATCTGAGGGTATCGCCCTCGA GGACCTGGCAGCGCTTCTGGGCACCCAGCGCGGGGGGCAGCAGGTGGTGCTGCGGAGAGGG AGCCCCTTCCGCGCCTCAATCCACATTCTGCCGCCTGGGCAGCCGCGCGCCCCACGCCT CCCTCCGCCTGCGGGGCCAGACGCCCTCCCTGGGGCCGGGGCGCAATCCACAAACGCT AATCTGATCCGACCTGCCGCCTGCCCCCTTGTGACCTGGTGCCGGGGGCCCTTCGCT AGACCAGGGGACACCCTCGGGGGCGGGCAATGAGAAATTTGCTGGAGTGCTCGGCCCCT CACTCCCTTCTGGAAAGTTCGAGATGTGTGCGGTGATGGACAGGCATCTG [SEQ ID NO: 143] - NODAL

FIG 2L

CAGATGCCTGTCCATCACCGCACACATCTCGAACTTTCCAGAAGGGAGTGAACTGGAAAA GCGCTCCCTCCTTTTTGCCCCCTCCCATCCCGGCCGCTTTTCGGTTGAGGGGCCGAG CAGATGACCCTTCCGGAGAGGGTCACCGGCTGTCTGACCCCAGGCGCGGGAGCGAAGGGC CCCCGGCACCAGGTCACAAGGGGCGGCAGGCGGCAGGTCGGATCAGATTAGCGTTTGTG GGCCGCGGCTGCCCAGGCGCAGAATGTGGATTGAGGCGCGGAAGGGGCTCCCTCTCCGC AGCACCCACCTGCTCGCCGCGCTGGGTGCCCAGAACGCGCTGCCAGGTCCTCGAGGGCGA TACCCTCAGATCCCTGCCGTCCTTGACACCCACTCCCCTGCAAATCATGGCCCCGAACCC GGGGTTAAGCGAGACACTTGACACTTCCCCGGCGGCTGGAGGACCCAAGGCTGCCACA GTTCGCGACTTCGGGACAGCCCATCCCTGATCTCCGGGCCGTGAGCCCGAATCCCCGATG TTACCAGCTCAGCTGCCGATACTCCCGACGTCACACCCCGGGACCCATTCACCCTCACTC GCAGAAAGAAAAAAATCGCCAAGACCAAACCATTACAGTAATACCAACGACCGTTGAC TGTGGCTGTGCCGGGTACTGCGCTGAGCGTTTCGCGCGCATTGTCATCTCGCGCTTTCCA CAGTCTGATAGGCGAGGTGTTATTTATTACACCTATCCTACAGATGCGCAGACCCAGGCT CCGGGATAAGCAACTTCACAAGACTGGAGATTAGAAGCTCCCACCCTTCCGCGCTGCGCT CCGCGCAATCCCAAACCAAAACCCAGAGACAATGGTCCCCGTCGAGGACACACCCTGAAC GCTAGAATCCCTTCCCGACTCGGCCGTGGATACGCCCCCAGCCACCAACGCTGCACCCG AGCCTGCTGACGCGGAGACACCCGCAGAGCTAGGCCCTGGGCTCGGGACGCCCGGGCGGC GACGCGGCGGAGGCCCCCGGGGGTGCCCAGCAGGGCGCGCACGCGGCACTGCCTACCT ATGTACGCCAGAGGGGTGGCGACGAGGGCTGCCCCGCGTACGCAGGAGCGCAGTGGCC TGGGCGTGCATGGTGGCCTGGCCAGGCCTGAAAGCAGCACCTCCAGCCCTTATATCCTGG GCCTCAGCAGCCGCCCCGCCCCACCTTTCCTCCCTCTGGGGAAGCTTTA

[SEQ ID NO: 144] - NODAL

 ${\tt ACCCCGGGGCGTGGGAGAGCCCCTGCTTGGGGGGGACCGTCTGCTGTTTAGGGGGCTCCCC}$ TTCGACACGTGGGAGGCAAAAGTGCAGAGCGCACCATCATCCAGCTCCGGCCGCACTGCA GTAAAGCAGAGGGGGCGAGGGAAGCCGGGCCAGCGGGTGTCGCGGGTAGCCGGCGTCCG GGACGGGTGTGCCCCAGAGCGCTGCTCCTCCCAGCCAGGAGGCTGGATGTCGGG TTTGGGTGTCTTCCAGAAGGAGCCGCACTAGCGACGAGGGAAGAGGAACTGGCTTCCCGG TGTGTCTTTAAATCTGAGCCCCCCGCCCCTCGCGGTGGGGCCGGGACTCGCGGTCCGGGC GGGGGCGGGCGGTGATTGGCGGCCGGGTCGGGTCCGCCCTCGGCGTTGGGTAGCGGG GCGCTGGGGAGCAGCGCGCGCGCACGGGCCGGGGCGCAGGTCCCCGTCGCCGGTGAGC AGGAGCACGGATGCCCCCGGAGCCGCGGCTGGCAGGTACCGAAGTGTCCTGCCCTGGG GCTGGCGAGGGGAGGCCAAATCTGGAATCCCCCGGGCACCCCCAGCCCGAGGCTGCTCC AGACACCAACTCCCATCCTTTGGAGAGGTGAGGTCCTGGGCCTTCACCCCACACCCGCT CAGGATTGGTCCCTGGGAGGCAAGAGGGAC

[SEQ ID NO: 145] - PALD

FIG 2M

GTCCCTCTTGCCTCCCAGGGACCAATCCTGAGCGGGTGTGGGGTGAAGGCCCAGGACCTC ACCTCTCCAAAGGATGGGGAGTTGGTGTCTGGAGCAGCCTCGGGCTGGGGGGTGCCCGGG GGATTCCAGATTTGCCCTCCCCTCGCCAGCCCCAGGGCAGGACACTTCGGTACCTGCCAG CCCGCGGCTCCGGGGGGCATCCGTGCTCCTGCGGCCGGCGTGCTGCGCCCGAACTGCGGG CCAACTTCGCCAGCCCATGCGGGGGCAGAGGTGGCTCCGGAGGTGGGCAGGCCAGGCGGA CCCGGCGAGGCCACGCGAGAGGGAGCCCGTGCTCACCGGCGACGGGACCTGCGCCCCG GCCCGTGCGCCCCCCCCCCCCCCCCCCCAACGCCGAGGGGCCGACCCG ACCCGGCCGCATCACCGCGCCCCCCGGCCCGGACCGCGGGCCCCACCGCG GGAGGAAAAGTTTGGGGCGGGGGAGACTGCCCGGGAAGCCAGTTCCTCTTCCCTCGTCGC TAGTGCGGCTCCTTCTGGAAGACACCCAAACCCGACATCCAGCCTCCTGGCTGCGAGAGG CAGCAGCGCTCTGGGCGCCACACCCCGTCCCGGACGCCGGCTACCCGCGACACCCGCTGG ${\tt CCCGGCTTCCCTCGCCCCCTCTGCTTTACAGCCAGGCCGAGCCTCGGCGGGACCGAGCC}$ CAGCATCCGGGCTCGGGCCGGCCTCGCTGTGCAGTGCGGCCGGAGCTGGATGATGGTGC GCTCTGCACTTTTGCCTCCCACGTGTCGAAGGGGAGCCCCTAAACAGCAGACGGTCCCCC CAAGCAGGGGCTTCTCCCACGCCCCGGGGT

[SEQ ID NO: 146] - PALD

CCGGAGCGGCGCGGCACCCCTGGGCTCTGAGGGGCGCTCTGAAGGGCGGCGGACTT CAGGGCCATGCTGGCTGTCCCCAGAAAGCAGGAGCCCGAAACCGCGGGGCCAACGAACGC ACAGGTAACGCCCAGAACGAGTGCTTCTCCCGGTGGGGTACTGAGGAGCCTGGGCTGCAG CTGCCGAGCCGCCACAGCCACGCTGAGCCCGGCCTGGCCTGCACACTGGCGCCACCGCCT GGCGGGGAGCGGACTGACGCGCTCCTCCCTCTCCAGCCCAGATCACGGAGGCGC GGAGCTCCATCTCCTGCCCTGGGCGAGGGGAGTGAGGGAGACAAAGACTTTGGGCACAAC ACCCACCACATAGAACCTATTCTCTAGTTGGGAAACAAGTCAAGGCAAAGGCGCACAGAG TGAAAGTCAG

[SEQ ID NO: 147] - LOC399783

CTGACTTTCACTCTGTGCGCCTTTGCCTTGACTTGTTTCCCAACTAGAGAATAGGTTCTA TGTGGTGGGTGTTGTCCCAAAGTCTTTGTCTCCCTCACTCCCCTCGCCCAGGGCAGGAG GGCTCGGCAGCTGCAGCCCAGGCTCCTCAGTACCCCACCGGGAGAAGCACTCGTTCTGGG CGTTACCTGTGGGGGCAGGGGGCAAGGGGAGAGGCGCAGGGGAGTTGTAGCA GAGAATGTGGGCGTTCGTTGGCCCCGCGGTTTCGGGCTCCTGCTTTCTGGGGACAGCCAG CATGGCCCTGAAGTCCGCCGCCCTTCAGAGCGCGCCCCTCAGAGCCCAGGGGTGCCCGCG CCCGCTCCGGTCCTCCGCCTTCTGCGGAAGGAAAACCAGGCCCTGGCTCGCTGGGACGG GTCCTTTCGG

[SEQ ID NO: 148] - LOC399783

FIG 2N

TCCCCCACCGAGCGCCCAACAAGTCTCCTTTCTCCAGCCTGCGCGCTGCTGCGCTGAGG TGGGACTGCGCCGTGCCCAGCCTCGGTCCCCTCTCTGTGGGTAAGGATGGTTGAGTCCAG $\tt CCTCCACGGCAGCGGCTCCTTGTGCCACTAGCAGCCCTTCTTCTGCGCTCTCCGCCTTTT$ CTCTCTAGACTGGATCTCTCCTCCCCCCGCGCCCCCTCCCCGCATCTCCCACTCGCTG CTTCTCCCCTCCGCAGCCTCGCCGCCTTGGTGCCTTCCTGCCCGGCTCGGCCGGCCG GTGGCTCGGGACCCGATGCTATGAGAGGGAAGCGAGCCGGGCGCCCAGACCTTCAGGAGG CGTCGGATGCGCGGGGTCTTGGGACCGGGCTCTCTCTCCCGGCTCGCCTTGCCCTCGGG TGATTATTTGGCTCCGCTCATAGCCCTGCCTTCCTCGGAGGAGCCATCGGTGTCGCGTGC GTGTGGAGTATCTGCAGACATGACTGCGTGGAGGAGATTCCAGTCGCTGCTCCTGCTTCT CGGGCTGCTGGTGCGCGAGGCTCCTCACTGCAGCGAAGGGTAAGACGGACTTGCT $\verb|CCTGGCCGGGGAGGCGGTAGAGCCCTCGGAGGCCCGTGTGCGGACGCGAGTGTGCGTTT| \\$ TGGGGACCGCAGGGTACGGAGTGGCCGCCTCTGCCCGGCGCTGCTCCATCGCCGAAGCTC GGGGAACGCGATGCACGGGAGGGAGCTTCCATCGCGCTCTCCCCAGCCCTCCTGGGCCCC $\tt CGCCCACCCGCCATTCCTTCCCCCTCTTTGGGCTCACAGGAGAGTCTCTTTTTCTC$ $\tt GGCAGTACAGGGTGTCAAGGAGAAAGGAACCCAATACGAGTTGGGCTGGAACTGTGCTCC$ GCCGGGCGGTGTTGCCTCCTCCGAGACGTGGACTCCACGGGTCGGGGTGGCTGAGGGGC GCCTGGAAAGTTCGGGCTCTCTACGGGGGTTTTGGTACCAATAGGCAAAGGTCTCCGCCG GCCCGGCCTCCTCGCACCCATACACCCCATTCCTCCTCTCCTCCTCCTCCAACGTC $\tt TTCGCTCCTTGCAAGTTGTAAGGTGTTGGCAAGGTGCGTGAAACAGGCTAGGAGTTCTGG$ ACCGGCTTCCAAGTCAGATACATTCACTGTGGGCGCACGGGTATCCTCCT

[SEQ ID NO: 149] - CSMD1

AGGAGGATACCCGTGCGCCCACAGTGAATGTATCTGACTTGGAAGCCGGTCCAGAACTCC TAGCCTGTTTCACGCACCTTGCCAACACCTTACAACTTGCAAGGAGCGAAGTCCGGGGGA GAGGAAAGCGGGGGCGACCTTCTAGAGGCAGCTACTCCTCGCCGGCTGAGGACGTTGGAG AGGGAAGGAGGAGGAGGATGGGGTGTATGGGTGCGAGGAGGCCGGGCCGGGGGAGACCTTTGCCTATTGGTACCAAAACCCCCGTAGAGAGCCCGAACTTTCCAGGCCGGCTTCACC CGGGACGCTTTCCCAGGCGCGTCGGGTCCGGGGAAAAGTCCTGGGAACTGCCCCTCAGC CACCCGACCGTGGAGTCCACGTCTCGGAGGAGGCAACACCGCCCCGGCGGAGCACAGT TCCAGCCCAACTCGTATTGGGTTCCTTTCTCCTTGACACCCTGTACTGCCGAGAAAAAGA GATCTCTCTGTGAGCCCAAGAGAGGGGGAAGGAATGGCGGGGTGGGGCGGGGGCCCAGG AGGGCTGGGGAGAGCGCGATGGAAGCTCCCTCCCGTGCATCGCGTTCCCCGAGCTTCGGC GATGGAGCACCCGGGCAGAGGCGGCCACTCCGTACCCTGCGGTCCCCAAAACGCACAC TCGCGTCCGCACACGGGGCCTCCGAGGGCTCTACCGCCTCCCCGGCCAGGAGCAAGTCCG TCTTACCCTTCGCTGCAGTGAGGAGCCTCGCGCACAGCCCGAGCAGCCCGAGAAGCAGGA $\tt CCGATGGCTCCTCCGAGGAAGGCAGGCCTATGAGCGGAGCCAAATAATCACCCGAGGGCA$ AGGCGAGCCGGAGAGAGCCCGGTCCCAAGACCCGCCGCATCCGACGCCTCCTGAAG GTCTGGGCGCCCGGCTCGCTTCCCTCTCATAGCATCGGGTCCCGAGCCACTGCAGGGCTG AGCTGCTCCGAGCGCGGAGACCCGGGCTGGCGGGGCCGGGGCCGGGCCCGGCC GAGCCGGGCAGGAAGGCACCAAGGCGGCGAGGCTGCGGGAGGGGGAGAAGCGGGGAGAGG GAGATGCGGGGGGGGGGGGGGGGGGGAGAGATCCAGTCTAGAGAGAAAAGGCGGA GAGCGCAGAAGAAGGGCTGCTAGTGGCACAAGGAGCCGCTGCCGTGGAGGCTGGACTCAA GCCCAGCCTCGGGCCTCGGGCTGCCGCACCGTGCTGCGCTTCATTCGGCCTCAGCGCA $\tt GCAGCGCAGGCTGGAGAAAGGAGACTTGTTGGGCGCTCGGGTGGGGGAAGCTCACGCC$ GCACACCGGGGAGGAACAATGTAATCCGGCAACTCCAGCAAACTGGAGGG

[SEQ ID NO: 150] - CSMD1

FIG 20

GGCATTGCCAGAGCGGCCTGTCCATGGGCAAGGGACAGCGACCTCCTGGGCCAGGACAT GTGAGAGCTGCGCAGGCCTGGGCCGGCGTGGCGGAGGTGCGCGAGAGCGGCCAGAAGAG GGCGCCAGAGAGCCAGGCGCGGCGCGGGAGGAGCCCGCGCCCCTATACCCAGCTC CGCGCCGCGCGCACCCACCGAGCCCGCGCTCAGACGCCCCAGCTCCACCGAGAGGCCGCT CGGGCCGTGTCCTTCTCTCCAGGTGCAGGCAGAGCCCCCGAGCCATGGCCAGCCCT GAGGACGACGTCCCTCCCGAAGAGAGAGGCTGGGGCTGTAGCTGGAGGGGGGAAGCGCA ACCCAGACAGGTGGCGACCGCAGAGGAGTAAGTGACGCGGGCCTGGGGTCCGGGGGTGC ${\tt CGGGGGCGCGGTAGGGGGGGGGGGGGGCTCGGTGGCCGGGCTGAAGTTGGTAT}$ TTTAGCGGCAACTCCGAAGGGCGCGGAGTGACAGCGCGTGACGGCCTCCGAGACGCCAGC AGACCCACTGGACTCTGCGGCTGGCCAAAAAGAGAGGGGCAGCCCGCGTCCTGGGGGCC $\tt CCCTGTTGGTGCCTCTCACCTGGCGAGGGGCCAGTGGTGGGGGGTAGGGGGGAAGTCCCTG$ GCGCCAGGCTTGGCCAAGCCCTGCTTGGCTGGACTGCGGGCTGGCGGCGCTCACCCAGCT CCTCACCTGTCCCGCATCTTCCTGTTTTTC

[SEQ ID NO: 151] - LOC441320

GAAAAACAGGAAGATGCGGGACAGGTGAGGAGCTGGGTGAGCCCGCCAGCCCGCAGTCC AGCCAAGCAGGGCTTGGCCAAGCCTGGCGCCAGGGACTTCCCCCCTACCCCCACCACTGG AGCGCAACACCCGCCACTTCCCCTGCTAGGGGCCCCCAGGACGCGGGGCTGCCCCTCTCT AAGTCAAAGCCACACGCCGAGAAGCGGCAGCTGGCGTCTCGGAGGCCGTCACGCGCTGT AGCCTCCCGCCCCTACCGGCGCCCCCGGCACCCCGGACCCCAGCGCCCGCGTCACT GTCCTCCCGTTCTCGCAGTCCTCGGGCTGTGCGCTTCCCCCCTCCAGCTACAGCCCCAG GGGCTTGCCAGTGGCTTCGGAGCTGCCGGAAGGGCTGGCCATGGCTCGGGGGGCTCTGCCT GCACCTGGAGAAGAGGAAGGACACGGCCCGAGCGCCTCTCGGTGGAGCTGGGGCGTCTG TCCGCGGGCCCCCTCTCTGGCCCCCTCTTCTGGCCGCTCTCGCGCACCTCCGCC ACGCCGGGCCCAGGCCTGCGCAGCTCTCACATGTCCTGGCCCAGGAGGTCGCTGTCCCTT GCCCATGGACAGGCCCGCTCTGGCAATGCCCTGCACCTCCTCCCCGCCCCGGCCAGGTTG CACCCGATGGTCTCCCTGCTCAAGGAGGA

[SEQ ID NO: 152] - LOC441320

FIG 2P

CCCAGTAAGTCACCAATTAAGTCTTTACTACTTAAAAGCAAAATCCACCTATGTCCTGAA TACATGTATACGTATACAAATATTTTCAAATTAAAAAAATACTTTTAGATAGTGGTATGT ATTACATTTAGAAATTAATAACGAAGTAAATTATGGGATGTCATCCACGCCTGTCCCAAA GGTACCGAATTTATAAATCATCTCAGGTGCGGAGCAGGACAGGTTGAAAATAGGAATGAC GCCCTCCAGCCCTGGGCCCGACCCCTACTACGCCTCTGCCTCGACGCGAACGCGGAGCC CGAGCGCGCGTCACGCCGTGTGGGGCCGAAGAGGCTGCTACCCAGAGGCGGAGTGCGGGC ${\tt TCGCGAGGGTCCCCACCCGACTCTCGCTCCCGCCAGCACCTACGGACTCGCGTCCCCGCC}$ GCGCGCCGACTCGGGAGCACCGCCCCCGGCACAGGAGCCTCACGCGCCTCTTACCTA ACAGGAAGTTGGGTGGAAGCAGCGCGGACCCACGGCACCCGAACGCACTCCAACAGAAC CCGACGCAGACACGCGCTTTCAACCGGCGGAGACACTGGCAGGGCCAGAAACGCGCGCAG CGGGGGCGGAGGTCGGTAAGCTCCCCGCCCTGCCCGAGACCCCGCCCCGGCCCGGCCC CGCCTTTTCTCTGCCTCCCTCCCTGCACGTACGGGCCCCGCCCCTCGCGCGACGTTTT TTGTTGACCCGGAAACGGATTCTCCGGAGCCGAGGTCCGCTCGGGTGAGTGCCCTCCGCT TTTTGTGGCCAAACCCAGCCACGCAGTTCCCTTCCTGCGGCGTCCTCCACACCCGGGGTC TGCTGGTCTCCGCGGATGTCACAGGCTCGGCAACCGCCCTCCTGTCGGCGGGGAGTCCCG CGACGCCCGGAAATGCTCCGAAGCCTGTCGCCCAGCTGCCAGATCTGCGTCTGTGTCCGG $\tt TTCCGTCACTGAGGTCGCCCTGTCCGGCCCTTCCACCCTAGTTCTCTTCACCGTCCGCC$ $\tt CATCCTATCGCGCGCGCCTCAGGTCCCGATTCGGCATGTGGCTTGTCTTCCATCGTCCC$ $\tt CACCCTCGCCCCTCTTGGCCCCTCAGGGCAGCCCTGGGATTCGGCAGACGCCAGTCCTCC$ CTGAGATGCTTCCCCATCCTTCCCTCCGCCAGGCCCTACG

[SEQ ID NO: 153] - ZNF596

ACATGCCGAATCGGGACCTGAGGCCGCGCGCGATAGGATGGGCGGACGGTGAAGAAACT AGGGTGGAAGGGCCGGACAGGGGCCACCTCAGTGACGGAACCGGACACAGACCCAGATCT GGCAGCTGGGCGACAGGCTTCGGAGCATTTCCGGGCGTCGCGGGACTCCCCGCCGACAGG AGGGCGGTTGCCGAGCCTGTGACATCCGCGGAGACCAGCAGACCCCGGGTGTGGAGGACG CCGCAGGAAGGGAACTGCGTGGCTGGGTTTGGCCACAAAAAGCGGAGGGCACTCACCCGA GCGGACCTCGGCTCCGGAGAATCCGTTTCCGGGTCAACAAAAAACGTCGCGCGAGGGGCG GGGCCCGTACGTGCAGGGAGGGAGGCAGAGAAAAAGGCGGGGCCGGGCCGGGCGGGGT CTCGGGCAGGGGGGGGGGTTACCGACCTCCCGCCCCCGCTGCGCGCGTTTCTGGCCCT GCCAGTGTCTCCGCCGGTTGAAAGCGCGTGTCTGCGTCGGGTTCTGTTGGAGTGCGTTCG GTGTGCCGTGGGTCCGCGCTGCTTCCACCCAACTTCCTGTTAGGTAAGAGGCGCGTGAGG CTCCTGTGCCGGGGCGGTGCTGCTCCCGAGTCGGCGCGCGGGGGGACGCGAGTCCGTA GGTGCTGGCGGAGCGAGAGTCGGGTGGGGACCCTCGCGAGCCCGCACTCCGCCTCTGGG TAGCAGCCTCTTCGGCCCCACACGGCGTGACGCGCTCGGGCTCCGCGTTCGCGTCGAG CCCTGGACACCGCGCGGCAGCTGTTCCGCGCGGGTTCATGTCATTCCTATTTTCAACCT GTCCTGCTCCGCACCTGAGATGATTTATAAATTCGGTACCTTTGGGACAGGCGTGGATGA $\tt TTATCTCGTACATATAATGAGGCTCGTAAAGTGGATACTGTTCAGGACATAGGTGGATTT$ TGCTTTTAAGTAGTAAAGACTTAATTGGTGACTTACTGGG

[SEQ ID NO: 154] - ZNF596

FIG 20

ACCGGCGTCCCGCTGGGGGCCCGAGGCCCCACCCCCAGAGATGCTGACTCAGCAAGTCG GGAGGGTTGGGGGTGGGACCTGCCAATCTGCATTTCCAACCGGCGCCCAGGTGACGCTG ACTCTGCTGGTCTACCGTCTTGGGGGTCACCTAATTTTTCAGCGATGCCTCCCAGCTGGG GAGGCCAAGAAGTGCCTCGCTCAAGGTCTTCCAACACCCGACCTCCAGACCCTCAATCCT GGGCCAGCTACACCGCAAACCTTTCCAGCTGTCTCTCCTGCGCCCTGCGTTTCTTCCCCA CGTCACTTGCCAGGGAGCCGCTAAACAGCAAGACCGCGCGCTCTGCGGCTCCAGAGTGCG CGCCATGGCTGCGCGCGGAGCCGGGCGATGCGCGCGGACTCTCCCGGGGCCCTGACTG GTCTGGCTGCGGGGTCTGCGGGCAGCTCCAACTCTGGGTTCGTAGTTTGCGCTGGGTG CGCAGGAAGGTCAGTGTGGGGGTCGCCCGACATTTCCCCCCCGCGGAGGTGGGAGCCGAG TGGTCGCAGAGTCAGGAGGGGGGGGCTCCGGAGCCCGGCGCGGGGAGGGCCCAGGCGCAGT CGGGGTTGGCAGGGCGCGACACTCGCTCCCCTCCACTTTTGAAAGGGCTTCCCACGCCGA GAAGAGGGGCGGCATGGCCGGCCGGCGAAACCGGTTTGTACAGACTTTGGGAAGCCAT CGCCTGCGGAGGGTGGGACCCCACAGCTTGTCCACCTGCCCAGGCTGAGACCTCGTGTCC TAGTCCTGGATGCCCCACGGGTTTCTCGTCCCGGGCAGCGCGCACGGGAGAGAAGACT $\tt CCCGGTCTGCAGTCAGACCTCCCTTGAGACCCTCCCTAGCTCAGGCTTAGAGCTTTGGG$ ATTTTTCTCGATCCTTTCTAGCTTTCAGATCATCCCCACGTAAAGTTCAGACTTTACCAG CCCAGAGAGTTTAAAAAAAAAAAAAAGAGAGAGAGAGAAAG

[SEQ ID NO: 155] - TDH

CTTTCTCTCTCTCTTTTTTTTTTTTTTAAACTCTCTGGGCTGGTAAAGTCTGAACTTTA CGTGGGGATGATCTGAAAGCTAGAAAGGATCGAGAAAAATCCCAAAGCTCTAAGCCTGAG CGCTGCCCGGGACGAGAAACCCGTGGGGCATCCAGGACTAGGACACGAGGTCTCAGCCTG GGCAGGTGGACAAGCTGTGGGGTCCCACCCTCCGCAGGCGATGGCTTCCCAAAGTCTGTA CAAACCGGTTTCGCCGGGCCGTCCATGCCCGCCCTCTTCTCGGCGTGGGAAGCCCTTTC AAAAGTGGAGGGAGCGAGTGTCGCGCCCTGCCAACCCCGACTGCGCCTGGGCCCTCCCC GCGCCGGGCTCCGGAGCCCCTCCTGACTCTGCGACCACGGCCGGGGACCCTGCGCGC GGCAACCCGCTCCGCGGCCAGTCCCACTCCAAGATGTGGCTCGGCTCCCACCTCCGCGG GGGGGAAATGTCGGGCGACCCCACACTGACCTTCCTGCGCACCCAGCGCAAACTACGAA CCCAGAGTTGGAGCTGCCCGCAGACCCCGCGCAGACCCCGCGCCTTTATCCCGCCC CGCCCGCCCGCCGGCGCACCAATCCCCGGCCGAGGAGGGGCCGCGTGGCGCGCGGG GGGCGGCCGCACGCCCCCGCAGGGAGGACTCAGGGACAGTCAGGGCCCCGGGAGAG GGATGGGGCGACGCGGTCAGAGCCGCACGCGACCGAAATCCGCACTCTGGAGCCGCAGAG CGCGCGGTCTTGCTGTTTAGCGGCTCCCTGGCAAGTGACGTGGGGAAGAAACGCAGGGCG CAGGAGAGACAGCTGGAAAGGTTTGCGGTGTAGCTGGCCCAGGATTGAGGGTCTGGAGGT $\tt CGGGTGTTGGAAGACCTTGAGCGAGGCACTTCTTGGCCTCCCAGCTGGGAGGCATCGCT$ GAAAAATTAGGTGACCCCCAAGACGGTAGACCAGCAGAGTCAGCGTCACCTGGGCGCCGG TTGGAAATGCAGATTGGCAGGTCCCACCCCAACCCCTCCCGACTTGCTGAGTCAGCATC TCTGGGGGTGGGGCTCGCGCGCCCCCAGCGGGACGCCGGT

[SEQ ID NO: 156] - TDH

FIG 2R

CTCATTTCGGGCCGCTTTTCTCAGAGGGCAAAGATGGGTCAGGGTGGGATGTTACATTAG TGTTGAGACTCTTTGGATCCGTTTCGTGGGTACCGAGGACGCCTGGGTACGCGGGACAGG $\tt CTGCACCGGCTGCTAGAGGCGCCCCATCGAGGCGCCACGGGTGAAGCTCCCGGCCCCAC$ CACGCCACGCGCAAAGGCGATCGCGACTCTCCTTCTGCAGGTAGCCTGGAAGGCTCTCT $\tt CTCTTTCTCTACGCCACCCTTTTCGTGGCACTGAAAAGCCCCGTCCTCTCCTCCCAGTCC$ CGCCTCCTCCGAGCGTTCCCCCTACTGCCTGGAATGGTGCGGTCCCAGGTCGCGGGTCAC GCGGCGGAGGGGCGTGCCCTGCCCCGGCCCAGCCGGCTCTTCTTTGCCTCTGCTGGAG TCCGGGGAGTGGCGTTGGCTGCTAGAGCGATGCCGGGCCGGAGTTGCGTCGCCTTAGTCC AGCCGAGGCGCAGAGAGGGGCGTGCAGGTGCGGGCGCGGATGGAGGCGCAGGTGTGGCGG CGCGAGCGGGTACAAGGAACACCTCGTGCTGGGCAGCTTCTTTACGGGGGTCTGTGGTTT CGTGCACAGGGGTGTGGGTGCAGAGCGGGCTGGCGAACCCCGTCCTCGGTAGATTCGGTG CTACCTGCAACTAGAACTCC

[SEQ ID NO: 157] - ASAH1

GGAGTTCTAGTTGCAGGTAGCACCGAATCTACCGAGGACGGGGTTCGCCAGCCCGCTCTG CACCCACACCCCTGTGCACGAAACCACAGACCCCCGTAAAGAAGCTGCCCAGCACGAGGT GTTCCTTGTACCCGCTCGCGCCGCCACACCTGCGCCTCCATCCGCGCCCGCACCTGCACG $\tt CCCCTCTCTGCGCCTCGGCTCAAGCTCACCGGCGGCGCGTGCTGCGCGACGGCACA$ GCTGACGGCGGCAGCCAGGAGGACTAAGGCGACGCAACTCCGGCCCGGCATCGCTCTAGC AGCCAACGCCACTCCCGGACTCCAGCAGAGGCAAAGAAGAGCCGGCTGGGCCGGGGGCA GGCCACGCCCCTCCGCCGCGTGACCCGCGACCTGGGACCGCACCATTCCAGGCAGTAGG GGGAACGCTCGGAGGAGGGGGACTGGGAGGAGGAGGGCCTTTTCAGTGCCACGAAA AGGGTGGCGTAGAGAAAGAGAGAGCCTTCCAGGCTACCTGCAGAAGGAGAGTCGCGAT CGCCTTTGGCGCGTGGCGTGATCCATCCCCCTCCCCCACCGCGGGCAATAGTCGGACCGA GCCGGAGCCCCGCCCCTAGGTGGGGCCGGGAGCTTCACCCGTGGCGCCTCGATGGGGCG CCTCTAGCAGGCGGTGCAGCCTGTCCCGCGTACCCAGGCGTCCTCGGTACCCACGAAAC GGATCCAAAGAGTCTCAACACTAATGTAACATCCCACCCTGACCCATCTTTGCCCTCTGA GAAAAGCGGCCCGAAATGAG

[SEQ ID NO: 158] - ASAH1

TGAGAGCTTCCCTGCCATTTCAGTGCAAAGTCCCTCCGGAGCGACCTCAGAGGAGTAACC GGGCCTTAACTTTTTGCGCTCGTTTTGCTATAATTTTTCTCTATCCACCTCCATCCCACC $\tt CCCACAACACTCTTTACTGGGGGGGTCTTTTGTGTTCCGGATCTCCCCCTCCATGGCTCC$ $\tt CTTAGCCGAAGTCGGGGGCTTTCTGGGCGGCCTGGAGGGCTTGGGCCAGCAGGTGGGTTC$ GCATTTCCTGTTGCCTCCTGCCGGGGAGCGCCCCCCTGCTGGGCGAGCGCAGGAGCGC GGCGGAGCGGGCGCGCGGGGCCGGGGGCTGCGCAGCTGGCGCACCTGCACGGCAT CCTGCGCCGCCGGCAGCTCTATTGCCGCACCGGCTTCCACCTGCAGATCCTGCCCGACGG CTGCCAAGGGCGTCATCGCCGCGGGGGCCCGGAGCTCCCCTGGACCCATCCGGTGCAAG ACGCAGGCTGGGGCTGAAGGGCTGGCCAGAGCAGCCGCGGGGAGAAATTTTCCTGCTGGT TTGTCGCCGCAGCCTCTAGCAGGGCAGCAGCTCCAGATGCTGGGGGCGGGAGGAAAGG GTGGGCGCTTCGCAAGCTCC

[SEQ ID NO: 159] - FGF20

FIG 2S

[SEQ ID NO: 160] - FGF20

CTTAACCCCCCATCTCCAGTTATCCCAATGAACCGACCCCGAGGGGGCATTTCCGCTGA AGTCCGGGGCTGTAAAAAATTAAGTGAGAAGAGCCGCGCTAAAGCCAAGCGTCGTCA $\verb|CCCAAGGTACTGCGCTGATGCGGTGCCGACCAGGTGCTCCCGCCGGGGCGTCTTCT||$ CCTACGCAGGAAGGCCACGCCGAGAGAGGCAGGCAACAAGGGCACGGCTGGAGGCCGGA AGGTCACCCCGTCCCCGGCGGGGCGGGCGCCCAGCCTCACTTCCCGGGCACGTTCGG GCGGGGCGATTGCAGGGAACGGGGGGGGGGGGGCGACAGTCCCCGGCTCCGCCGCGCCCA GCCCGCTTCGCTGCCCGGAGGCCCGCAGGCCTGGGTTCCCGGACAGCTGAGCCCGAGC CGCGGGCGGTCTCCCGACGGCTGTCGCGGGGCCCACCCCAAAGCCCCCGATCCCCGGTAGC TGCGCTTCCCGCGGGGGCGCCGGAGTAGGGCGGGCCAAGCTGGCCTGCGGCCGCGGCGG CGGCCACGCGCACCCTGCCGCCCGCACCCCGCGCGCCCTCCGTCTATTTTTTCCTCT TCCTTTCATCCTCACACTCTAAAATAGGTCAAGGGGTGGAAGTTACACCTGGTGCAGCCC TCGGCTCTGATGCAAAAGCAGCTTTTGCCCCTGGCTGCGGGACAGCGCTGTGACTACTCG $\tt CAACGGGAGAGCTGCTGCCAGTCGCCACACCGTGCGGAAAGCGCCGGCGACCGGAGCACT$ GACAATGGTCTGCATAGGGGAGCGGAGAGAGCTTCTGTTGCGCCCTAGATCCGCTGCCT CGGCGCCCGCCGCAGGGAGGGGGGCGCGACAGGTCGTCTAGCGCGTGCCCCGGAGCC $\tt CGCGCCCGGGTCTGGCCGCCTGGGTGAGTTCCTGCTCGTCCCTGCCTTTCCAGTAGCCC$ GGGGTGGCTGTTTACCTTGCAAACAGCCTTGCAATACGATCAAAACAGGCGAGACAGCCA TGCAGTAAGGGATTGCGGGATGTGCTTTGGGTGTGAGATTGGATAAATCAGAATTCAGAG ATAAAGGACATGTCTAGTGCCTTAAGGGTTAAAGTGGATT

[SEQ ID NO: 161] - FLJ36980

FIG 2T

AATCCACTTTAACCCTTAAGGCACTAGACATGTCCTTTATCTCTGAATTCTGATTTATCC AATCTCACACCCAAAGCACATCCCGCAATCCCTTACTGCATGGCTGTCTCGCCTGTTTTG ATCGTATTGCAAGGCTGTTTGCAAGGTAAACAGCCACCCCGGGCTACTGGAAAGGCAGGG GACGAGCAGGAACTCACCCAGGCGGCCAGACCCGGGCGCGGGCTCCGGGGCACGCGCTAG ACGACCTGTCGCGCCCCTCCTCCTGCGGGCGGCCGAGGCAGCGGATCTAGGGCGC AACAGAAGCTTCTCCCGCTCCCCTATGCAGACCATTGTCAGTGCTCCGGTCGCCGGCGC TTTCCGCACGGTGTGGCGACTGGCAGCACTCTCCCGTTGCGAGTAGTCACAGCGCTGTC $\verb|CCGCAGCCAGGGGCAAAAGCTGCTTTTGCATCAGAGCCGAGGGCTGCACCAGGTGTAACT|\\$ TCCACCCCTTGACCTATTTTAGAGTGTGAGGATGAAAGGAAGAGGAAAAAAATAGACGGAG CCGGGGCTCGTGTCGGGGCTTCCAAAGAGAAGTTGCAGCGAGGCGCCCCCCGGCGTCCGG CGCCTGGGCCCGGTCGGGGTGCTTCGCTAGCCCTTCTTCCCGCCGCGGCCGCAGGCCAG TTGGGCTGGCCCGCGACAGCCGTCGGGAGACCGCCCGCGCCCCCGCCCCCGTCACCGT CCCCGCCTCCCGGGCCGCCTTCACCTTTCGGGAGGCGCGCTCGGGCTCAGCTGTCCGG AGGCTGGGCCGCCCGCCGCGGGGACGGGTGACCTTCCGGCCTCCAGCCGTGCCC TTGTTGCCTGCCTCTCGGCGTGGCCCTTCCTGCGTAGGAGAAGACGCCCCGGCGGGAG CACCTGGTCGGCCCGCAGCGCATCAGCGCAGTACCTTGGGTGACGACGACGCTTGGCTTT AGCGCGGCTCTTCTCACTTAATTTTTTTACAGCCCCGGACTTCAGCGGAAATGCCCCCTCG GGGTCGGTTCATTGGGATAACTGGAGATGGGGGGGTTAAG

[SEQ ID NO: 162] - FLJ36980

CTAGCATTTACTGGATTCCAGAGTCTTGTTATTTAAGAATGCATCTTAAACGGTACTATC AAATTCATGTTACGTGCAGCCCAGATTGTTTTGGGCAGCACGAAAAGTTTCTGAGGCGCT GCGTGTACCCCACCCCAGGACACCGTGTGTGCGCGCCGAGCTGAGTGCGAGGAACGTGGC GCGAGGCCGGGGGTGCCGGCTGCGTGAGCCCTCGCGCGACCGCGACCCCGC GCCTCTCCCGCTCTCGCCGGAACGTGACCGCAGCCGCACCTCTCCTCCAGCCCTTTCCCA GCCAGACGCTTCCTTTTAGGTCCTTCTGGGCGTTTATTGTAAATTCTGCGACTAAAACAC GCCGGTGAGCCCGCCCACCGACAGATGGATCAATCGCCCCCTTCCCGGCTAGGGGAGGA GGAACCCCCAACCCGGAGCCTAGGGAGCCGGGAGCTGCCTCGGGACGAGCTCCTCGGA GCCCAGCCGGCTGCGGAGCCCCGGCCCGGGTCTCTCGGGGGCCCTCCTGCCGGGGTGGG GGTGGTCAGGGCCCTGGCCCAGCAGGCTTCTTCCCGAGCCGGGGGGAGGGGAACCGG GGGCGTGAGGCCAAAGTTCCCGAGGTCCGCGCGAGAGCACACGTGTATGTGCGCGCGGG GGATAATTCCTTTCCCTGGCACCATCGGGGAGACGCTTTGTCGGCCTCGGCTCCTGGGCG CAGGGACGCCTTAGCCCACGGAGGGTGGAGCCCCCTCAGACCCGGGCCACCGGCTGGGG TTTTTCTAACGCCCTGCCCCCGAGCCCCCGGATGGCTCGGGCCCCACGGACTCCGCGCC GAGGAGGAGGTGCCGACGCTTGAGTGGGTTCGAGCCCGAGCCGTAGCCGGGGGAGCCAG TCAGTTTCCGGCCAAGGCAGCAGGTCAGTCCCAGGAAGGGCGGCGATTGAGCCGAGGGA GCCGGCGGCTGGGCTCTCCTCTCGGCCCGCGATCCCCGGCGCCGCCGCCGCCGCCACCGC CTCCCGCGCCCCGCGCCCGCGCCGCGCCTGGGAGCCCGAGCCCGAGCCCGGGG CGGAGGAGAGGGCCTGGCGCGAGAGCCCGGGCGAGGGAGCCGCGAAGGGAAAGGGGG AGAAAGACACGCACGCAGAGACACACGGTCACTGGAATTCCATTAGAAAAAAGTGAGC CGAGCAAGGGTTAGCGGGAGAAGATTTTTTTGAATCTTGTCTTCGTCTTGGTGCGAAAGA AGCGACTCCAGTCTCTCGTCCTCGAAGCTCCGACTGGATTGTTCTTGGGCGCTGACACCC [SEQ ID NO: 163] - GFRA2

FIG 2U

GGGTGTCAGCGCCCAAGAACAATCCAGTCGGAGCTTCGAGGACGAGAGACTGGAGTCGCT TCTTTCGCACCAAGACGAAGACAAGATTCAAAAAAATCTTCTCCCGCTAACCCTTGCTCG CTCTCCTCTCTCTCTCTCTCCCTCGCTCGCTCTTTGCTCTCGCTCTCTCCAGCTC CCCCTTCTCCCTTCGCGGCTCCCTCGCCCGGGCTCTCGCGCCAGCGCCCCTCTCCTCCG CGCGGCGGAGCTACGATGCTCTGCAGCGGCGGCGACAAGGCGAAGGCGGTGGCGGTG GCGGTGGCGGCGGCGGCCGGGGATCGCGGGCCGAGAGGAGAGCCCAGCCGCCGGC TCCCTCGGCTCAATCGCCCGCCCTTCCTGGGACTGACCTGCTGCCTTGGCCGGAAACTGA CTCCCCCGCAGCTCTCCCCACCCTGGGGACCGGCTGCGCCCTCCAACCCCCACTGCCCC TGCCCCGCCCCTGCGCCGCTGGGTCTGGGAAGCCTGGGGAGCTGAGCTGAGCTGGAG GGCGCGGAGTCCGTGGGGCCCGAGCCATCCGGGGGGCTCGGGGGGCCAGGGCGTTAGAAAAA $\tt CCCCAGCCGGTGGCCCGGGTCTGAGGGGGGTCCACCCTCGTGGGCTAAGGCGTCCCTG$ CGCCCAGGAGCCGACAAAGCGTCTCCCCGATGGTGCCAGGGAAAGGAATTATCC $\verb|CCTTCGGCGCCCCGGCGCCCCCGAACCCAACGCATCCTGCCGGCCCCGGCCTAGC| \\$ $\tt CCCGCGCGCACATACACGTGTGCTCTCCGCGCGGACCTCGGGAACTTTGCCCTCACGCCC$ GCGGCGCGCTTCCCGCCCGCCCCGGCCTCCACCCCTTCGAGATGCCCCTTCCCCAG ${\tt CCGGTCTCCCCTCCCCCGGCTCGGGAAGAAGCCTGCTGGGCCAGGGCGCCCTGACCACCC}$ TCCTCGGAGGCCGGCAAACCTGCCTGAACCGCCCCAGAGGAATCGGGCAGGGGCTCGCAC $\verb|CCCACCCGGCAGGAGGGCCCGAGACCGGGCCGGGGCTCCGCAGCCGGCTGGGC| \\$ ${\tt TCCGAGGAGCTCCCGAGGCAGCTCCCGGCTCCCTAGGCTCCGGGGTTGGGGGGTTCC}$ GTGTTTTAGTCGCAGAATTTACAATAAACGCCCAGAAGGACCTAAAAGGAAGCGTCTGGC TGGGAAAGGGCTGGAGGAGAGGTGCGGCTGCGGTCACGTTCCGGCGAGAGCGGGAGAGGC GCGGGGTCGCGCGCGAGGGCTCACACCCACGCAGCCCGGCATCCCCCGGCCCTCGC GCCACGTTCCTCGCACTCAGCTCGGCGCGCACACACGGTGTCCTGGGGTGGGGTACACGC AGCGCCTCAGAAACTTTTCGTGCTGCCCAAAACAATCTGGGCTGCACGTAACATGAATTT GATAGTACCGTTTAAGATGCATTCTTAAATAACAAGACTCTGGAATCCAGTAAATGCTAG [SEQ ID NO: 164] - GFRA2

AAACAGCATTAGCCTTCTCCCATCAAAAGTCCGGAAGCTGCCCTTCAGTCGTCAAAGTGT TTGCCTTAATTTGCAATCGTTATGACTTGAGCCAAATGCTTATACCTCATTTGTGTCGTA TATGTGAAGATACAATTGCAAATCGTTCACGACCTTGAGTCAAGACCTTGAGTTTCCTGA GGTCAGGAGACCGTTAGGGAATGTGAGTGTCCCAGACGGGCGCTGAGCCCAGCTCGGAGA CCCACCCGCCGTAGCAGCGGCGCGGGCCCCAGAGAGCCCCGCACTCGGCCGCGCCTCA GTTACGCTGACTCGGCTGTGCCCGCAGTGTCGCGCTGTCGCGTAGCCAGGTGTCGCCGGG GGATCCGCCGCCTCTTCCATGATCTTCCCGGGCCGAACCACGGGACCGCTACGCTGAAGG TCTTGTGGCCGCCACCCGGGTGTCTCCTCCACTCTGCGCTCACCAGCCCCTCCTTGGGC TGAGCGTGGCGGCGGCGGCGGGGGGGCTGGTCGGCCTGGTATGCTACCAGCTGTACG GGGACCCCAGGGCCGGCTCGCCGGCGACCGGGCGACCCTCAAAGAGCGCGGCCACGGAGC CCGAGGACCCGCCCCGCGGCGGGGGATGCTGCCCATCCCAGTGGCGGCTGCCAAGGAGA GCAGGACCCTGGAGGCTGTGGGGACGTTCCAAGCGCTGTGGCCGCGGGTGAGGAACTTCC CGTGAGCGAGGCTGACACCTAGGCCGGACAGCCTAGGATCCGGTCACCCACGTATTGGGA AGACCAGTGATGCTGTCCCTGATGCATCAGGACCTTAAAGGTGGCTGCAGCTACCAAGTA TCAATCCAAACCCAAAACCAACACCCCTCCCCCTCTTACA

[SEQ ID NO: 165] - EFHA2

FIG 2V

TGTAAGAGGGGGAGGGTGTTGGTTTTGGGTTTGGATTGATACTTGGTAGCTGCAGCCAC CTTTAAGGTCCTGATGCATCAGGGACAGCATCACTGGTCTTCCCAATACGTGGGTGACCG GATCCTAGGCTGTCCGGCCTAGGTGTCAGCCTCGCTCACGGGAAGTTCCTCACCCGCGGC ATCCCCGCGCAGGTGTGACGCGCGCTCGCGCACTCACCGTCTCCTTGGCAGCCGCCACT GGGATGGGCAGCATCCCCCGGCCGCGGGGCGGTCCTCGGGCTCCGTGGCCGCGCTCTTT GAGGGTCGCCGGTCGCCGGCGAGCCGGCCCTGGGGTCCCCGTACAGCTGGTAGCATACC AGGCCGACCAGCCCCCGCCGCCGCCGCCGCCACGCTCAGCTCCCCCAGCGCCGCCGC CGCCTCCATGCCGCCTCCGCCACAGCCCTCTCCTCATCCTCTCGGGAGGAGAAGGGCCGG CCAGGAAGGCCCAGGGTGGTCACCGCAGGCCGCCCCCACGGCCCAAGGAGGGGCTGGTGA GCGCAGAGTGGAGGAGACACCCGGGGTGGCGGCCACAAGAGCCTTCGCAGCGCAGCCATA GGGGGGTCGCCGAAATCTCGCGAGAAGTCGGTGCCGCGAGCTTCGCGGCCGACGAGAGC GACCCTACACTCGCGCGGCCCCGGGGACCCGCGACGCTCAGCGTAGCGGTCCCG TGGTTCGGCCCGGGAAGATCATGGAAGAGGCGGCGGATCCCGGCTGCTCCCCGGCCCCGA ACCCCAGCCCAACCACGCAGTCATAAATAACCGCGCCAGCCCGGCGACACCTGGCTACG CGACAGCGCGACACTGCGGGCACAGCCGAGTCAGCGTAACTGAGGCGCGGCCGAGTGCGG GGCTCTCTGGGGCCCGCCGCTGCTACGGGCGGGTGGGTCTCCGAGCTGGGCTCAGCG CCCGTCTGGGACACTCACATTCCCTAACGGTCTCCTGACCTCAGGAAACTCAAGGTCTTG ACTCAAGGTCGTGAACGATTTGCAATTGTATCTTCACATATACGACACAAATGAGGTATA AGCATTTGGCTCAAGTCATAACGATTGCAAATTAAGGCAAACACTTTGACGACTGAAGGG CAGCTTCCGGACTTTTGATGGGAGAAGGCTAATGCTGTTT

[SEQ ID NO: 166] - EFHA2

GTTAGTTCCGGTCCCTTCCCCTCCCCACTTGGACGCGCTTGCGGAGGATTGCGTT GACGAGACTCTTATTTATTGTCACCAACCTGTGGTGGAATTTGCAGTTGCACATTGGATC TGATTCGCCCCGCCCGAATGACGCCTGCCCGGAGGCAGTGAAAGTACAGCCGCCGCCCC CCAAGTCAGCCTGGACACATAAATCAGCACGCGGCCGGAGAACCCCGCAATCTCTGCGCC CACAAAATACACCGACGATGCCCGATCTACTTTAAGGGCTGAAACCCACGGGCCTGAGAG ACTATAAGAGCGTTCCCTACCGCCATGGAACAACGGGGACAGAACGCCCCGGCCGCTTCG CGGGTCCCCAAGACCCTTGTGCTCGTTGTCGCCGCGGTCCTGCTGTTGGTGAGTCCCCGC CGCGGTCCCTGGCTGGGGAAGAGCGTGCCTGGCGCCTGGAGAGGGCAGGGAGAGAGGGGG CAGTCGTCGGAGTCGGGGAAGAGATGGGTCCCCGGGTTGGGCAGGAGCGACCTGGGCCG CCAGGGAACAGAGCGCGCTCCACTTGGTGTAAATTCCCGAATCCAGTGGGGGAGGGCG ACAAGGAGGGAATTCCCGAGTAAGCTGCGTGAAGCCACGGAGAGGTCGTCGGACTTTGAT TGGTCGCTGCGGCCCAGTGGTTCCGTTCCGTGCGCGGGAGTCGTCGCGGGCCGCAGCTGGA GAGGCCCCTTCCCTTAGCGGCTGCGCCCCTACGCGTGCGGGGCCGCTCATCGCCAA TGCCATTGTTTGGGGTTCCTTGGGAAAACGAGATTTAGGAGAAGGGAGTTGTGGCACTTG GGGCCTGACCTGCTTGATAATAGCAGCTGCATTTTTGGCCTGGGAAGAGCCTTTCTTGCCA CCTCTTGGCAAGTATCCGTGATAATGGGGAAGGGACAAAG

[SEQ ID NO: 167] - TNFRSF10B

FIG 2W

CTTTGTCCCTTCCCCATTATCACGGATACTTGCCAAGAGGTGGCAAGAAAGGCTCTTCCC AGGCCAAAATGCAGCTGCTATTATCAAGCAGGTCAGGCCCCAAGTGCCACAACTCCCTTC TCCTAAATCTCGTTTTCCCAAGGAACCCCAAACAATGGCATTGGCGATGAGCGGCCCCGC ACGCGTAGGGGCGCAGCCGCTAAGGAGGGGGAAGGGGCCTCTCCAGCTGCGCCCGCGACGA CTCCCGCGCACGGAACGGAACCACTGGGCCGCAGCGACCACAGGGGAGTTCTTCGCCGGC GAAAAAGAGAAAGAAACAGAAAGTAAGGAAAGAAAACAAAATCAAAGTCCGACGACCTCT CCGTGGCTTCACGCAGCTTACTCGGGAATTCCCTCCTTGTCGCCCTCCCCCACTGGATTC GGGAATTTACACCAAGTGGAGCGCGCGCTCTGTTCCCTGGCGGCCCAGGTCGCTCCTGCC CAACCCGGGGACCCATCTCTTCCCCCGACTCCGACGACTGGTGCGTCTTGCCCGGACATG CCCGGCCGCAGGCGACCCGGGCCACCCCGCCGTGTCCCCTCTCTCCCTGCCCTC TCCAGGCGCCAGGCACGCTCTTCCCCAGCCAGGGACCGCGGGGGACTCACCAACAGCA GGACCGCGGCGACAACGAGCACAAGGGTCTTGGGGACCCGGGGCCCAGGCCTGGCTCCCC GCGCCTCCCTGGGTCCTGGGCCGTGCCTTTTCCGGGCCCCCGAAGCGGCCGGGGCGTTCT GTCCCCGTTGTTCCATGGCGGTAGGGAACGCTCTTATAGTCTCTCAGGCCCGTGGGTTTC AGCCCTTAAAGTAGATCGGGCATCGTCGGTGTATTTTGTGGGCCCAGAGATTGCGGGGTT $\tt CTCCGGCCGCGTGCTGATTTATGTGTCCAGGCTGACTTGGGGCGGCGGCGGCTGTACTTTC$ ACTGCCTCCGGGCAGGCGTCATTCGGGGCGGGGCGAATCAGATCCAATGTGCAACTGCAA ATTCCACCACAGGTTGGTGACAATAAATAAGAGTCTCGTCAACGCAATCCTCCGCAAGCG $\tt CGTCCAAGTGGGGAGGGAGGGAAGGGACCGGAACTAACCTTCGCCCTGGCGGCTGCGC$ CCCGGGCTGTGGTTTGTTTCTGGGTCCTGTCCGCGCCAGG

[SEQ ID NO: 168] - TNFRSF10B

TGCCCCTTTTCTGAGTGCTTGGAAGTGACTGCTGCAAGTGACAAGTGACCACGCCTTTTC $\tt CTCTCCACGCGCACGAACTCAGCCAACGATTTCTGATAGATTTTTGGGAGTTTGACCAGA$ GATGCAAGGGGTGAAGGAGCGCTTCCTACCGTTAGGGAACTCTGGGGACAGAGCGCCCCG GCCGCCTGATGGCCGAGGCAGGGTGCGACCCAGGACCCAGGACGGCGTCGGGAACCATAC GCAGGACGAACTCGCCGTCGGAGTCAGGGGAAGAACTGGGTCCCCGGGCTGGGCAGGAGG GACCCGGCCGAGGGAGCAGAGAGGCGGTCCCCCTGGCTGCCCCGAGCCCGCGAAGGGA GGGAAGTTCCAGAATCGAGAGAGGGAGGGAGTCAAGGTGGAACCCATAGAGTGAGCCTCC CATGTTTACATTCTTAAACGTGTTCCTTGGAGATCGGTTTAACCAACAGCCAGTGAAAAA ACTTTTCAGCGCTGTCTTTA

[SEQ ID NO: 169] - TNFRSF10C

TAAAGACAGCGCTGAAAAGTTTTTTCACTGGCTGTTGGTTAAACCGATCTCCAAGGAACA TGCTCCCTCGCGGCCGGGTCCCTCCTGCCCAGCCCGGGGACCCAGTTCTTCCCCTGACTC CGACGCCGAGTTCGTCCTGCCCGGACATGCCCGGCCGCAGGTGACCAGGGCCAGGCATCC GACCGCGGCCGGACTCACTGGCAGCAGGACCGCGACGATGACGACGACGAACTTTAGGG TCTTGGGGATCCGGGCCATGGTATGGTTCCCGACGCCGTCCTGGGTCCTGGGTCGCACCC TGCCTCGGCCATCAGGCGGCCGGGGCGCTCTGTCCCCAGAGTTCCCTAACGGTAGGAAGC GCTCCTTCACCCCTTGCATCTCTGGTCAAAACTCCCAAAAATCTATCAGAAATCGTTGGCT GAGTTCGTGCGCGTGGAGAGGTTCCCACAGCTGCACTGCCAGAATCGGAGCGCAGCGCCT $\tt CTGAATTTATACCCGCGGGGGAAAAGGCGTGGTCACTTGTCACTTGCAGCAGTCACTTCC$ AAGCACTCAGAAAAGGGGCA

[SEQ ID NO: 170] - TNFRSF10C

FIG 2X

GAAATAACTTGAGCCAGGGATCAAACACTAAGATTGGCAGGAAATGAGCAGGAAGAGGTA GCGGGGTCCCTGACGCCATCTATTCAATTGTTTTTCAGAAGAGGTATCAGCTCTTGAAGG CTTACTTCTCAATACTGGCTGCGAGAGCAAGAATGGTGTGTAATTTACAAAAGCCGTCAT TGCTGTAGGTAAGTTGTAGCAAACGACTCGCGCCCGAGCATTCCCGCCCCCGCCTTCGCT GCGCCCCGCCCACGACGACCCTGGGGAACTACAAGTCCCGCCATACAGCGGGGAGCGCC CGGAGCTCGCGCCCGCCCCCAGCCCGGTCCCCACCCCGGCTCCGCCCCCGGCCC CCTCCCGCCGGGTCAACCCCGAAGAGTCGCCGGTGGCCGCGGCAGACGGAAGCCGAACGA GTTCCTCGGCGGCTGCAGGATGGGGGACTCCAAAGTGAAAGTGGCGGTGCGGATACGACC CATGAACCGGCGAGGTGAGAGCCGAGCCCTCCTGGGCCGCGGGGCGGAGGCGGCAGGTG CCTGGCGCGCCCTTCCCTCGGCCGCCGTGGGGGGTCCGGCGCCCCTATAGTCAG CGGCGGGGCGAGGAGGGCCCGGGGACCCTGAAACCCGCTCCCGCGCTGAGACGCCCG GCTCCCTCTTCTCCCCTCCCTTCCCCCCTGGCCAGCCCCGTCCCTGGCGCCCGTCGGGCCC $\tt CTCTCGTCTCCCCCGGAGGTTCCCGAGGGCGCCCTCGGCCCTCGCGCCCAGCCTCGTCCT$ CAGCCCTGCAGCCCGCCTCGGGACCGCCGGGACCCCCGGGACCCCGCGTCTCGCCCG GGTCGCCCAAGCCTGCACCGCCTTGGCCCGCGGCGGAAGAAGGGCCAGGGGGCCAGGCGG GTGCCCGCGGCGAGTTCCTTCCACCTGGGCGTCCTGAGATTGGGGTCAGGTGGAGGAGA TGCCCTTTTCGTTGTTTTTGGACAGTTGAGAAAGTTTTGGTTTTTGCCTGAAGTCTCATTC ATCATCTCTCAATAAATAGCTAAAGTGCCAAGATTCTTGTGGAATTGTATCTTTCTGACA TTCTCTTAACTCTGCAGGGAGTGTAGAGAAGGCAGATAAACCGAGTACATTTAAATAATC TGTAGACCCGGGGAGTGGAGAGACCCCAAAAGTCAGGGG

[SEQ ID NO: 171] - KIF13B

CCCCTGACTTTTGGGGTTCTCCCCCCGGGTCTACAGATTATTTAAATGTACTCGG TTTATCTGCCTTCTCACACTCCCTGCAGAGTTAAGAGAATGTCAGAAAGATACAATTCC CCAAAACTTTCTCAACTGTCCAAAAACAACGAAAAGGGCATCTCCTCCACCTGACCCCAA TCTCAGGACGCCCAGGTGGAAGGAACTCGCCGCGGGGCACCCGCCTGGCCCCTT $\tt CTTCCCGCCGGGGCCAAGGCGTGCAGGCTTGGGCGACCCGGGCGAGACGCGGGGTCCC$ ACGATGACAGCTGGCGGGAAGGAGCGAGGCTGAGGGCCCAGGACGAGGCTGGGCGCGAG GGCCGAGGGCGCCTCGGGAACCTCCGGGGGAGACGAGAGGGCAAAAGGGCGCAGGGGCG GGGCGGCGCAGGGGAAGGGGCCAGGGGCCCGACGGCGCCAGGGA CGGGGCTGGCCAGGGGGAAGGGAGGGAGAAGAGGGAGCCGGGCGTCTCAGCGCGGGAG CGGGTTTCAGGGTCCCCGGGCCCTCCTCGCGCCCCGCCGCTGACTATAGGGGCGGGGCC GCCGGACCCCCACGGCGGCCGAGGGAAGGGCGCCCAGGCACCTGCCGCCCCCG GCGGCCCAGGAGGGCTCGGCTCTCACCTCGCCGGTTCATGGGTCGTATCCGCACCGCCAC TTTCACTTTGGAGTCCCCCATCCTGCAGCCGCCGAGGAACTCGTTCGGCTTCCGTCTGCC GGTGGGGACCGGGCTGGGGGCGGGCGCGAGCTCCGGGCGCTCTATGGC TGCTCGGGCGCGAGTCGTTTGCTACAACTTACCTACAGCAATGACGGCTTTTGTAAATTA ${\tt CACACCATTCTTGCTCTCGCAGCCAGTATTGAGAAGTAAGCCTTCAAGAGCTGATACCTC}$ TTCTGAAAAACAATTGAATAGATGGCGTCAGGGACCCCGCTACCTCTTCCTGCTCATTTC $\tt CTGCCAATCTTAGTGTTTGATCCCTGGCTCAAGTTATTTC$

[SEO ID NO: 172] - KIF13B

FIG 2Y

ACCCCTCCTTCCTTCTTTCCCTACCGCCCCACGCGCGACCCGGGGATGGCTCCGTGGCC TCACGAGAACAGCTCTCTTGCCCCATGGCCGGACCTCCCCACCCTGGCGCCCAATACCGC GCTGGCGGTGCTGGCCACCGTGGGAGGCAACCTGCTGGTCATCGTGGCCATCGCCTGGAC TCCGAGACTCCAGACCATGACCAACGTGTTCGTGACTTCGCTGGCCGCAGCCGACCTGGT GATGGGACTCCTGGTGGTGCCGCCGGCGGCCACCTTGGCGCTGACTGGCCACTGGCCGTT CGAAACCCTGTGCGCCCTGGCCGTGGACCGCTACCTGGCTGTGACCAACCCGCTGCGTTA $\tt CGGCGCACTGGTCACCAAGCGCTGCGCCCGGACAGCTGTGGTCCTGGTGTGGGTCGTGTC$ GGCCGCGTGTCGTTTGCGCCCATCATGAGCCAGTGGTGGCGCGTAGGGGCCGACGCCGA GGCGCAGCGCTGCCACCCGCGCTGCTGTGCCTTCGCCTCCAACATGCCCTACGT GCTGCTGTCCTCCGTCTCCTTCTACCTTCCTCTTCTCGTGATGCTCTTCGTCTACGC GCGGGTTTTCGTGGTGGCTACGCGCCAGCTGCGCTTGCTGCGCGGGGAGCTGGGCCGCTT TCCGCCGAGGAGTCTCCGCCGGCCCGTCGCGCTCTCTGGCCCCGGCCCCGGTGGGGAC GTGCGCTCCGCCGAAGGGGTGCCCGCCTGCGGCCGGCGCCCCGCGCGCCTCCTGCCTCT $\tt CCGGGAACACCGGGCCCTGTGCACCTTGGGTCTCATCATGGGCACCTTCACTCTGCTG$ GTTGCCCTTCTTTCTGGCCAACGTGCTGCGCGCCCTGGGGGGCCCCTCTCTAGTCCCGGG ${\tt CCCGGCTTTCCTTGCCCTGAACTGGCTAGGTTATGCCAATTCTGCCTTCAACCCGCTCAT}$ $\verb|CTACTGCCGCAGCCCGGACTTTCGCAGCGCCTTCCGCCGTCTTCTGTGCCGCTGCGGCCG|\\$ ${\tt TCGCCTGCCTCGGAGCCCTGCGCCGCCGGCCCGGCCCTCTTCCCCTCGGGCGTTCC}$ $\tt CGGGGCAGAGGGACCGGCGCTCAGGGTCGGGAAGCATGCGATGTCCGTGGGTCAACT$ GGTAGAAGCAAAGGAGGGCGAGCGGGCCGTCGTTCCTCACCCAAGGACCCAAGGTGCGCC ACCGGAAAGCGCTGCGGTGTCCCGAGGACTCTCGCCTCGCCTGGTCGGCT

[SEQ ID NO: 173] - ADRB3

 ${\tt AGCCGACCAGGCGAGGGCGAGGTCCTCGGGACACCGCAGCGCTTTCCGGTGGCGCACCTT}$ GGGTCCTTGGGTGAGGAACGACGGCCCGCTCGCCTCCTTTGCTTCTACCCTAGTGACTG GATCCGGAAAGAAAAGGACCCTGGGTCCCATTTTGGTTCGCTACTCCTCGTTCCCTTTTC TCTCCAAGCAAAGCCATCCCACCTTCTCTTAATAAACTCCACACTCAAAAAGTTGACCCA GGCACAGAAGACGCGGAAGGCGCTGCGAAAGTCCGGGCTGCGCAGTAGATGAGCGGGT TGAAGGCAGAATTGGCATAACCTAGCCAGTTCAGGGCAAGGAAAGCCGGGCCCGGGACTA TGAAGGTGCCCATGATGAGACCCAAGGTGCACAGGGCCCGGTGTTCCCGGAGAGGCAGGA GGCGCGGGGCCGCCGCCGCAGGCGGCACCCCTTCGGGCGGAGCGCACGTCCCCACCG GGGCCGGGGCCAGAGAGCGCGACGGCGGCGGAGACTCCTCGGGCGGAAAGCGGCCCA GCTCCCCGCGCAGCAAGCGCAGCTGGCGCGTAGCCACCACGAAAACCCGCGCGTAGACGA AGAGCATCACGAGAAGAGGAAGGTAGAAGGAGGACGGAGGACAGCACGTAGGGCA TGTTGGAGGCGAAGGCACAGCGCGGGTTGGAGTGGCAGCGCTGCGCCTCGGCGTCGG CCCCTACGCGCCACCACTGGCTCATGATGGGCGCAAACGACACCGCGGCCGACACGACCC ACACCAGGACCACAGCTGTCCGGGCGCAGCGCTTGGTGACCAGTGCGCCGTAACGCAGCG GGTTGGTCACAGCCAGGTAGCGGTCCACGGCCAGGGCGCACAGGGTTTCGATGCTGGCGG TCACACACAGCACGTCCACCGAGGTCCACAGCTCGCAGCCAGTGGCGCCCAACGGCCAGT GGCCAGTCAGCGCCAAGGTGGCCGCCGGCGCACCACCAGGAGTCCCATCACCAGGTCGG CTGCGGCCAGCGAAGTCACGAACACGTTGGTCATGGTCTGGAGTCTCGGAGTCCAGGCGA TGGCCACGATGACCAGCAGGTTGCCTCCCACGGTGGCCAGCACCGCCAGCACCAGCAGCAGCAGCAGGG $\verb|CCCGGCTAGGGCCGCCTCCCACGGAACCCCTGGCAGCCCACTGGTGTTGGCGGTATTGG| \\$ GCGCCAGGGTGGGGAGGTCCGGCCATGGGGCAAGAGAGCTGTTCTCGTGAGGCCACGGAG [SEQ ID NO: 174] - ADRB3

FIG 2Z

CGCAGACCCAGCAGGAGAGCGCAACCTAGCATCTTTAAGGTTCGCTTAGCCCTTCCTGTG CACCTGGAAGGAAGCCTTATCTTAAACTCCCTTCCACCTAGAGTTTATTTTCGCCTGCGT GCGACAGGGCTTTTGTACTTAAGTGAGTTAAGGAATGAACCCCGAACTCTTCTGGGAAAG CCACCAACGTTCCCCCGCACCCCTCCCAGGGTTCCTGACCACGGAGACTCTGCTTGGGG GAGCAGCCTCCCAGGCGCTGCCTGGCTGCGGAGGGGAGCGGCAGCGAGAGCCTCGGGT CTCCGCCTGGGTTCCCGGGTCTCCGGGCCTCGGTCTCCGCGCAGCGTCCAGCG AAAAGGGGCTGCCCGGGAGCCCGAGCCCAGGCTCCTCCCGGTGGCGTGTCCGCGCCT GCGCCTGCCTCCAACCTGCGGGCGGGAGGTGGGTGGCTGCGGGGCCAATTGAAAAAGAGCC GGCGAGGAGTTCCCCGAAACTTGTTGGAACTCCGGGCTCGCGCGGAGGCCAGGAGCTGAG CGGCGGCGGCTGCCGGACGATGGGAGCGTGAGCAGGACGGTGATAACCTCTCCCCGATCG GGTTGCGAGGCCCGGGCAGAGCCAGGACGCGAGCCGCCAGCGGTGGGACCCATCGAC GACTTCCCGGGGCGACAGGACCCCCGAGAGCCAGGGCGAGCGCCCGTTCCAGGTGGC CGGACCGCCGCGCGCCCCCCCCCCCCCCCCGCGCAACGGGAGACGCCCCCGCGCA GCGCGAGCGCCTCAGCGCGCCCTCGCTCTCCCCCTCGAGGGACAAACTTTTCCCAAAC ${\tt CCGATCCGAGCCCTTGGACCAAACTCGCCTGCGCCGAGAGCCGTCCGCGTAGAGCGCTCC}$ GCAGCGCGGCCCGGGCCCCACGATCCTCCTCCTCCTCCTCCTCCTCCTCCTCCTCCTCGG ATGCCGTGGCCTCTCCCTCTCCCTCGCCCGTCCTCTTCGCCCTGCGCTCTGAGC GCCCGTTGAGTCGCGCGGTGCTTCCCCTCCTGGGGGCCGCCGCTCACCTGGGCGCCGAGT CCTACCGGGCGCCTACGCCCAGAGCTCAGGGCAAGGGACAGCAGTCCCGGCCGCACCCTC CCAGAGTCCCGGGAGCGCTTCGCTCCCTGGCACGCCCCTCCCCAGCGCCTTAGCGGCTG GCGCCATAAGCGCTTTGCACGGGGGCCGTGTGCCCTCTAGCGGGAAACGCTGGAATGGGC TGCGCGCCGGTTCATCTTGATTCAGTCCTGTGCTACGGAGACTCAAGAGCAGCGGCAGGG [SEQ ID NO: 175] - NRG1

FIG 2AA

CCCTGCCGCTGCTCTTGAGTCTCCGTAGCACAGGACTGAATCAAGATGAACCGGCGCGCA CTCTACATCGCTTGCCCTGTGCCCCAAAACGCCGAAGCTAACTTCCCACGCGGCCTCTTG GCCCATTCCAGCGTTTCCCGCTAGAGGGCACACGGCCCCGTGCAAAGCGCTTATGGCGC GGGGCACGCGCACGCAGCCTCGACTCCTATAGCCCAGGTCCCACTCCCGGGCTGGGCT CAGCCGCTAAGGCGCTGGGGAGGGCCGTGCCAGGGAGCGAAGCGCTCCCGGGACTCTGG GAGGGTGCGGCCGGGACTGCTGTCCCTTGCCCTGAGCTCTGGGCGTAGGCGCCCGGTAGG ACTCGGCGCCCAGGTGAGCGCCGCGCCCCAGGAGGGGAAGCACCGCGCGACTCAACGGGC GCTCAGAGCGCAGGGCGAAGAGGCCGGGCGAGGGAGGGGAGGGCCACGGCAT CCGAGGAGGAGGAGTAGGAGGAGCAGGAGGATCGTGGGGCCCGGGCCGCGCTGC GCACCCACCTGGGCTCTGCCCGCCGCGGACTCCGGCTTCTTGCCGGAGCCTCGCTC CTTCTTCTTGCCCTTTGCCTCTGCCTTCTTTTGCGCTCGGACATCTCGCCGGAGAC GGAGCGCTCTACGCGGACGGCTCTCGGCGCAGGCGAGTTTGGTCCAAGGGCTCGGATCGG GTTTGGGAAAAGTTTGTCCCTCGAGGGGGAGAGCGAGCGCCGCGCTGAGGCGCTCGCGC GCCACCTGGAACGGCCCTCGCCCTGGCTCTCGGGGCTGCTCCTGTCGCCCCGGGAAGTC GTCGATGGGTCCCACCGCTGGCGGCTCCTGGCCTCTGCCCGGCGCCCTCGCAACC CGATCGGGGAGAGGTTATCACCGTCCTGCTCACGCTCCCATCGTCCGGCAGCCGCCG $\tt CTCAGCTCCTGGCCTCCGCGCGAGCCCGGAGTTCCAACAAGTTTCGGGGAACTCCTCGCC$ CTCCTTCGCACCCTCCCCTGGCCTCGCCCCCTCCTTTCCCCACCACACCCCCACCCCG AGGCGCGGACACCCCGGGAGGAGCCTGGGCTCCGGGCGCTCCCGGGCCCCTTTT CCTCCCGCGCTGGCCGGGCGGGGGTGGCGGCGGCTGCCGGAACCCCCGACAGGGGT CGCTGGACGCTGCGCGGAGACCGAGGCCAGCGCCCCGGAGACCCGGGAACCCAGGCGGAG ACCCGAGGCTCTCGCTGCCGCTCCCCTCCGCAGCCAGGCGCCTGGGAGGGCTGCTC CGTCCCATTCCACGCGGAAAAGGACGGCGCAGAGAAAAGTTTGCGACTCCCACACCTGTG $\tt CTTTCCCAGAAGAGTTCGGGGTTCATTCCTTAACTCACTTAAGTACAAAAGCCCTGTCGC$ CACAGGAAGGGCTAAGCGAACCTTAAAGATGCTAGGTTGCGCTCTCCTGCTGGGTCTGCG [SEQ ID NO: 176] - NRG1

FIG 2BB

GGGAGGGTGGCCTGCAAGGCGGGGCCGGTTGCGGTCAAGTTCAAGTAGGGTCAGAGCAGG AGAACACTGGCATAAAAAATAGCCACATCCAAGGAAGCAGTGAGGTGTGGGGACCATCTA TTTCGGTGGGCCTTCCCACCCCAGGCCGGCCTTCCCATCACGCGTGGGTGTGGGGGCAC TGCCCCGCTGCGCGCAGGAACAGCGGGGAGAGCCAGGAGCGGCTTCGGGATGCC AGACTGAGCAGTGGGTTCGTCTGCGGCCACCTCTCAGGGAACAAGCTTCCCCCCGCGGAG ACTCTGCTTCTTTTAAAAGCCTTCCTGGGTTTAGTCTAGGGCGACAGGACGACCTCCCTT GGGAAGGGAGACCTGCCAGTCCCCTCCCATTCGCCAGGCGGTGCAGCCCCTCCTCCCG CCCGGGGCGCGCACCTCAGCGTCGCGGGCCTAGCGCCCAGCAGCCGCCCCAGGCCG GCGGGGCCGAGTCGCGAAGCGCGCCTGCGACCCGGCGTCCGGGCGCGCTGGAGAGGACG ${\tt CGAGGAGCCATGAGGCGCCAGCCTGCGAAGGTGGCGCGCTGCTGCTCTGGGCTGCTCTTG}$ GAGGTAGGGGCCGGGGACCGGGTGCTGCCGGAGGCGCGCCCACCATGCTGGCGGCTG GGGGCGCGCAGTTCCGAGGCGCCCCAGAGGACCTTGCCTGGGAGCGCAGACGGTGGAGCG ACGGGGAGCCACAGCCCTGCGCGCCTCCCGGAGCTGGGAGGTGCGGGACCCTGGTGACGG GGAGGCTCCCGCCCGGTCCGCCCTTCCGTCGTTCCTTCGGTTTTCGCACCCCGCCCCC ACCCTGCGGGTGAGCGCGTTTCCCGCGCCGACCGCCTCCGTTAGCTCGGGGTGACCTTTG TGCACCGTCCGCCCTCTCCCCGCCGCAGAGGGCCGAGGATCGGATGGACCCGGGGTTG GGCGGGGTGGTCCTCGGGCGCGCGCGCGCGGGGGGGGGCGCGGGCAGTTTG GGGTTAGGAAAGGATGGGTGCCGAGCCGGGGTGAGGGGAGCGGCGGAGGGGACTGTGGG GAAGTGTCGCGGGAGTGCCGGGAGTTGTGGAGGTGAGCAGCGGGAGGAGGCGTTCCCGCG GTGGGGTGCGGAGCCGAAGCCGGCGGGAACTTGTTGAGCGGCTTCCGGGTGCGAGCGC CCGTGACCGCATCCCTGGCGGGGACCGCGGCTGCTCCTGGCTGTGAAATTGCATCCTCGG ATGGGGCCACATACTTCTCACTAAAGCAGGTTCCTTAAAATGCGAACTAG [SEQ ID NO: 177] - ECOP

CTAGTTCGCATTTTAAGGAACCTGCTTTAGTGAGAAGTATGTGGCCCCATCCGAGGATGC AATTTCACAGCCAGGAGCAGCCGCGGTCCCCGCCAGGGATGCGGTCACGGGCGCTCGCAC TCTCCGCAGAATTTCCTCCCCGCACCTAAAGGCTGCACTTCATTTTCACACGCGGGAACG CCTCCTCCCGCTGCTCACCTCCACAACTCCCGGCACTCCCGCGACACTTCCCCACAGTCC CCTCCGCCCGCTCCCCTCACCCCGGCTCGGCACCCATCCTTTCCTAACCCCAAACTGCCC GGCGCCCGGGCTCTCCGCGCCTGCGCCGCGCCCGAGGACCACCCCGCCCAACCCCGGG CCCGAGCTAACGGAGGCGGTCGGCGGGGAAACGCGCTCACCCGCAGGGTGGGGGCGGG GGTCCCGCACCTCCCAGCTCCGGGAGGCGCCAGGGCTGTGGCTCCCCGTCGCTCCACCG TCTGCGCTCCCAGGCAAGGTCCTCTGGGGCGCCTCGGAACTGCGCGCCCCAGCCGCCAG CATGGTGGGCGCCGCCTCCGGCAGCACCCGGTCCCCGGCCCCTACCTCCAAGAGCAGC $\tt CCGAGCAGCGCCGCCACCTTCGCAGGCTGGCGCCTCATGGCTCCTCGCGTCCTCCC$ AGCGCGCCGGACGCCGGGTCGCAGGCGCGCTTCGCGACTCGGCCCCCGCGCGGGGGCGGG CGGGCAGACTGCAGCCGGAGCCGTCCCGCCGACCGCTGGGGGGCCCGGCTGGGAGCGG CGGGAGCCGGGCGCGCGCAGCCCTGGCTCCGCCCCCGGCCGCCGCGCGCTC GGCTGCACCGCCTGGCGAATGGGAGGGGGACTGGCAGGCTCTCCCTTCCCAAGGGAGGTC GTCCTGTCGCCCTAGACTAAACCCAGGAAGGCTTTTAAAAGAAGCAGAGTCTCCGCGGGG GGAAGCTTGTTCCCTGAGAGGTGGCCGCAGACGAACCCACTGCTCAGTCTGGCATCCCGA AGCCGCTCCGCTCCTGCCTCTCCCCGCTGTTCCTGCGCGCAGCGGGGGCAGTGCCCCCAC ACCCACGCGTGATGGGAAGGCCGGCCTGGGGGTGGGAAGGCCCACCGAAATAGATGGTCC CCCTACTTGAACTTGACCGCAACCGGCCCCGCCTTGCAGGCCACCCTCCC

[SEQ ID NO: 178] - ECOP

FIG 2CC

TGCTGGGCAATGCGTGGTGGTGGCTGCCATCGCCTTGGAGCGCTCCCTGCAGAACGTGG ${\tt CCAATTATCTTATTGGCTCTTTGGCGGTCACCGACCTCATGGTGTCGGTGTTGGTGCTGC}$ CCATGGCCGCGCTGTATCAGGTGCTCAACAAGTGGACACTGGGCCAGGTAACCTGCGACC CGCTGGACAGGTACTGGGCCATCACGGACCCCATCGACTACGTGAACAAGAGGACGCCCC GGCGCCCCCTCCTCATCTCGCTCACTTGGCTTATTGGCTTCCTCATCTCTATCCCGC CCATGCTGGGCTGGCGCACCCCGGAAGACCGCTCGGACCCCGACGCATGCACCATTAGCA TGCTGGTTCTCTATGGGCGCATATTCCGAGCTGCGCGCTTCCGCATCCGCAAGACGGTCA AAAAGGTGGAGAGACCGGAGCGGACACCCGCCATGGAGCATCTCCCGCCCCGCAGCCCA AGAAGAGTGTGAATGGAGAGTCGGGGGAGCAGGAACTGGAGGCTGGGCGTGGAGAGCAAGG $\mathtt{CTGGGGGTGCTCTGTGCGCCAATGGCGCGGTGAGGCAAGGTGACGATGGCGCCCCTGG}$ AGGTGATCGAGGTGCACCGAGTGGGCAACTCCAAAGAGCACTTGCCTCTGCCCAGCGAGG CTGGTCCTACCCCTTGTGCC

[SEQ ID NO: 179] - HTR1A

GGCACAAGGGGTAGGACCAGCCTCGCTGGGCAGAGGCAAGTGCTCTTTGGAGTTGCCCAC ${\tt TCGGTGCACCTCGATCACCTCCAGGGCGGCGCCATCGTCACCTTGCCTCACCGCGCCATT}$ GGCGCACAGAGCACCCCAGCCTTGCTCTCCACGCCCAGCCTCCAGTTCCTGCTCCCCGA TCCGGTCTTCTCCACCTTTTTGACCGTCTTGCGGATGCGGAAGCGCGCAGCTCGGAATAT GCGCCCATAGAGAACCAGCATGAGCAGCAGCGGGATGTAGAAAGCTCCAAAGGTGGAATA GATAGTGTAGCCATGATCCTTGCTAATGGTGCATGCGTCGGGGTCCGAGCGGTCTTCCGG GGTGCGCCAGCCCAGCATGGGCGGGATAGAGATGAGGAAGCCAATAAGCCAAGTGAGCGA GATGAGCGCAGCGGCGCCGGGGCGTCCTCTTGTTCACGTAGTCGATGGGGTCCGTGAT CTGATACAGCGCGGCCATGGGCAGCACCAACACCGACACCATGAGGTCGGTGACCGCCAA AGAGCCAATAAGATAATTGGCCACGTTCTGCAGGGAGCGCTCCAAGGCGATGGCAGCCAC CACGCACGCATTGCCCAGCA

[SEQ ID NO: 180] - HTR1A

TGACGCAAGGTCCAGATTGCCAGGCCCGGGGCATGAGAGAGGATCCTTGTAGGTT TCGGAGGTGGGGGGCTCCACTCCATTGTTCACTCCGGGCCAATCAGGGTTGGCCCACTT CCTGGATCCCCATCACCTCCCCGCATCCCCGGCAGTTCTGGGGAAGCTTCGTGACGCCA GAGGCCGGGCGCGACCCTCGTCCTTCTGCCCCTGGCCGCACACTTTGCGCACATCTCT TTTTCTGCATGGTGGATATTATTTTTCATTATCCTTTTCTGGGTGCTATGGGTGATCATT AAATTTCTAA

[SEQ ID NO: 181] - ISL2

FIG 2DD

TTACTCTTGGAATGATCACCCATAGCACCCAGAAAAGGATAATGAAAAATAATATCCACC ATGCAGAAAAAGAGTGTGCGCAAAGTGTGCGGCCAGGGGCAGAAGGACGAGGGTCGCGC GCCCGGCCTCGGCTCTTTGCTAACTACTCCTACTGCCCCGCGGAGTTGAAGGAGCGATT CCGCACCGGCCCGCACGCATGACGTCAACACGCACTAGCCCCGGGCCGGAGCTGGGG GCGGGACCTGTGGCGTCACGAAGCTTCCCCAGAACTGCCGGGGATGCGGGGGAGGTGATG GGGATCCAGGGGCTGATGGGCGGGGTGGGTTGGGTTGGAGGCTGGGGGTGAAGGGAGATT GGCTGGGAGGAAGTGGGCCAACCCTGATTGGCCCGGAGTGAACAATGGAGTGCAGCCCCC CCACCTCCGAAACCTACAAGGATCCTCTCTCATGCCCCGGGCCTGGCAATCTGGACTGGA CCTTGCGTCA

[SEQ ID NO: 182] - ISL2

CAGGGAACAGACCCAGTAGTTGGCTTGGATCTCTTAACTCCAGAAAAAGGCCGAGTGAGGA CAAGGGAGACCACAGGGATAATTTCTGTGGCTCTGGTAAGGGGATGACAAGGGAGAAAAA CGCCGCCCACGCGGCTCGGGTGGGAACCCGCAGACGTGGGGCGAGCAGGGCCGCTGGC TGTGGCGGGCGAGCGCCGGGGCGCCACGTCCGAGGCCGCGGGGTCGGGGCTGCAGGCACA GCTCGAGCGCTTTCCGCGGGGTTTGGCTCCTGTCGCTTCCCGTCTCGCCGAACCGGCATC GCCGCCGGAGCCGAGTCCTCAGAGCCTGGCTGCTGGCGGCCGGAGCGCCGG GACGGGGCGCGAAGCCGGAGGCTCCGGGACGTGGATACAGGTAAAGGCCGGCGGGTCGGA GTCGGGCGGGCGCGCGCCCTCTCGGAGGGACCTGGCCTCGGCCGGGCCCTACC $\tt CAGCCGCGGTGCCCGGGCCCCCACGTTGGCCCAGGCGGGACGTGCCAAGGGGCTGGGC$ TAGGGTTGCCGCTGGCCTGCCCCCCCCGGCGGGCCTCAGGTGACGCGGCCGCGG CTTAACTTTCGCACCTGAGGCTCTCGGAGCGCCTCGGGGCGCCCCACCTGGAGGTTGG AATTACACAGGGTCGAAAAAGCTGAGTCCTGGAGGCGAGGCGCTGTAGGTGTGGCGGAGG AGGCCGGGGAAGGTGGGTGGGTGCCAGGGGTCCAGTACTGAACCCTCTCCAGGTCTGAG GTGGGGAACTGCGTCTTGTTTAATTTCGGAGCTTGTGGGGACCACACACCCCTTCCACG GCCGATTCCCTCTGCACGGTTCCACTTTCCTTTGTCTAGCCCATTTCAGTATCGGCGTCG CAGTCGCTTTTGTTGCAGCCTTGGGTCCGGAGTGTACGACTTTCTGCTAGGCAGAGGTCA TAAGCTCTGAAATCCATCGGGCGGAGGTGG

[SEQ ID NO: 183] - LOC285671

 $\tt CCACCTCCGCCCGATGGATTTCAGAGCTTATGACCTCTGCCTAGCAGAAAGTCGTACACT$ CCGGACCCAAGGCTGCAACAAAAGCGACTGCGACGCCGATACTGAAATGGGCTAGACAAA GGAAAGTGGAACCGTGCAGAGGGAATCGGCCGTGGAAGGGGCTGTGTGGTCCCCACAAGC TCCGAAATTAAACAAGACGCAGTTCCCCACCTCAGACCTGGAGAGGGTTCAGTACTGGAC CCCTGGCACCCCACCTTCCCCGGCCTCCTCCGCCACACCTACAGCGCCTCGCCTCC AGGACTCAGCTTTTTCGACCCTGTGTAATTCCAACCTCCAGGTGGGCGCCCCGAGGCC GCTCCGAGAGCCTCAGGTGCGAAAGTTAAGCCGCGGCCGCGTCACCTGAGGCCCGCCGGG CGAGAGGCGGCCAGCCGGCAACCCTAGCCCAGCCCCTTGGCACGTCCCCGCCTGGG $\verb|CCAACGTGGGGCCCGGCCACCGCGGCTGGGTAGGGCCCGGCCGAGGCCAGGTCCCTCC||$ GAGAGGCGCCGCCGCCCCCCCCGACTCCGACCCGCCGGCCTTTACCTGTATCCAC GTCCCGGAGCCTCCGGCTTCGCGCCCCGTCCCGGCCGCCGCCAGCAGCCAGGCT GGAGCCAAACCCCGCGGAAAGCGCTCGAGCTGTGCCTGCAGCCCCGACCCCGCGGCCTCG GACGTGGCGCCCGGCGCCCCCCCCACGCCCCCTGCTCGCCCCACGTCTGCG CGCCGCGGGCCAGACGGAACCGTGGGAAAGTTTTTCTCCCTTGTCATCCCCTTACCAGAG CCACAGAAATTATCCCTGTGGTCTCCCTTGTCCTCACTCGGCCTTTTCTGGAGTTAAGAG ATCCAAGCCAACTACTGGGTCTGTTCCCTG

[SEQ ID NO: 184] - LOC285671

FIG 2EE

GGCAGCAGCCGCTGGCTTCTGCGCCCACTAGGAGCTTCGGATGCCCGAGTTAGGGCTGCG CCAAGGCGGCCGGAGCAGAGAGGGAGACGGGGACGGGACAGGCAGGGACAAGTGCAAG AGGCAAAACTGGCTGAAAAGCAGAAGTGTAGGAGCCGCCAAGGGGCGGACGAACAGGTC TAGTCCCCAGCCTCCCTTCCCCCGGCCCTGATTGGCAGGCGGCCTGCGACCAGCCGC GAACGCCACAGCGCCCCGGGCGCCCAGGAGAACGCGAACGGCCCCCGCGGGAGCGGCC AGTAGGAGGGGCCCGGGCTATATATATAGCGGCTCGGCCTCGGGCGGCCTGGCGCTC AGGGAGGCGCACTGCTCCTCAGAGTCCCAGCTCCAGCCGCGCGCTTTCCGCCCGGCTC GCCGCTCCATGCAGCCGGGGTAGAGCCCGGCGCCCGGGGGCCCCGTCGCTTGCCTCCCGC ACCTCCTCGGTTGCCCACTCCTGCCCGAGGTCGCCGTGCGCTCCCGCGGGACGCCACAG GGGCCGGGATGTCGGGGCCCGGGACGCCGCGGTAGCGCTGCTCCCGGCGGTCCTGCTGG CCTTGCTGGCGCCCTGGGCGGGCCGAGGGGGCGCCGCACCCACTGCACCCAACGGCA CGCTGGAGGCCGAGCTGGAGCGCCGCTGGGAGAGCCTGGTGGCGCTCTCGTTGGCGCGCC TGCCGGTGGCAGCCCAAGGAGGCGGCCGTCCAGAGCGGCGCCGGCGACTACCTGC GCCAGGCGCAAGGGGCGGGGGGGGGCCAACCCGCTCAGTCAC ACTCTGAGACCCTCGGCGGCACCTGCTCGGGGGCCCCGGGAACCGGGGCGGACTCGGGC TCCGGTCCCTTCTGACGCGGGGCTGGGGACGCAGACACTCTTGGCTCCGGCAGCCCAGCG CAACCCCTGAGGTCGGGCGCCGCCTCCCGCCTTCAGAAACTCGGGCTCCGAGCGCCGAAT TCCAGCGCCTTCGCCCGTGGGCACAGGGCGCGCGCGTGCAGCCACAGGGGGCCCGAGACAC GCGCCCGGCCTGGCCCAGGCTGGGGAACCGCTGGGGTCGGGCTCTGAAGGTCCG GGACTGGGTGCGCCGGGGGGTCCCCTACACAGGCAAGCTAATCTGAGCTAGCGCAGG $\tt CTTGGGCTCCGGAGGCCCTAGAGGGCAGCTTGGGGCCCTTGGGGGGCGGCTGC$ GCCGGGAACCCTGGCCCTTTATCCCCAACCCCACCCCAGAAATAGGGTCCCCGGAGGCGA ACAAGCCGAGGGCGGAGTGGGCCAGGGATCACCTGCCCCGCAATGACCTGCGCCCCGCC CCCAGGCCTGCTGGAGCTCTCGCCCGTGGAGCGGGGGGTGGTGAGCATCTTCGGCGTGGC ${\tt CAGCCGGTTCTTCGTGGCCATGAGCAGCAAGGGCAAGCTCTATGGCTCGGTGAGTACCGC}$ AGGGGTCTGGCTAGGCACCTAGTTGGGAACAGCGGACATGGCTAGCAGGCTCGTGGCTTC [SEQ ID NO: 185] - FGF4

FIG 2FF

GAAGCCACGAGCCTGCTAGCCATGTCCGCTGTTCCCAACTAGGTGCCTAGCCAGACCCCT GCGGTACTCACCGAGCCATAGAGCTTGCCCTTGCTGCTCATGGCCACGAAGAACCGGCTG GCCACGCCGAAGATGCTCACCACGCCCCGCTCCACGGGCGAGAGCTCCAGCAGGCCTGGG GGCGGGGCGCAGGTCATTGCGGGGCCAGGTGATCCCTGGCCCACTCCGCCCCTCGGCTTGT ${\tt TCGCCTCCGGGGACCCTATTTCTGGGGTGGGGTTGGGGATAAAGGGCCAGGGTTCCCGGC}$ GCAGCCGCCCCAAGGGCCTCCAGAGCCCAAGCTGCCCTCTAGGGCCTCCGGAGCCCAAG CCTGCGCTAGCTCAGATTAGCTTGCCTGTGTAGGGGACCCCCGGCGGCCGCACCCAGTCC GTGTCTCGGGCCCCTGTGGCTGCACCGCGCGCCCTGTGCCCACGGGCGAAGGCGCTGGA ATTCGGCGCTCGGAGCCCGAGTTTCTGAAGGCGGGGGGGCGCCCGACCTCAGGGGTTG CGCTGGGCTGCCGGAGCCAAGAGTGTCTGCGTCCCCAGCCCCGCGTCAGAAGGGACCGGA GCCCGAGTCCGCCCGGTTCCCGGGGCCCCCGAGCAGTGCCCGCCGAGGGTCTCAGAGT GTGACTGAGCGGGTTGGCCCGGCGCCGTTGCCCCCGCCCCGCCCCTTCGCGCCTGGC CGCGCCACTCACTGTCGCGGGTGTCCGCGTGCGCCGCCGATGCGGCCGTCGGGGAGCG $\tt CCTGGAGGTGGAAGCCGATGCCCACGTTGCAGTAGAGCCGCCGCAGCCGCTTGATGCCCA$ GCAGGTAGTCGCCGCCCCCTCTGGACGCCCCCTCCTTGGGCTGCGCTGCCACCGGCA GGCGCGCCAACGAGAGCGCCACCAGGCTCTCCCAGCGGCGCTCCAGCTCGGCCTCCAGCG GAGGGCCGTGCGTCAGGCGGTCAGTGCGCCCGGGAAGCTGGGGGGCAGAGCTGCGC CTGTGGCGTCCCGCGGGAGCGCACGGCCGACCTCGGGCAGGAGTGCGCAACCGAGGAGGT GCGGGAGCCAAGCGACGGGCCCCGGGCGCCCGGCTCTACCCCGGCTGCATGGAGCGGC GAGCCGGGCGGAAAGCGCGCGGCTGGAGCTGGGACTCTGAGGAGCAGTGCGCGCCTCCCT GAGCGCCAGGCCCGAGGCCGAGCCGCTATATATATAGCCCGGCGCCCCCTCCTACT CGCCGCTCCCGCGGGGGCCGTTCGCGTTCTCCTGGGCGCCCCGGGGCGCTGTGGCGTTC GCGCTGGTCGCAGGCCGCCTGCCAATCAGGGCCGGGGAAGGGAGGAGGCTGGGGACTA GCGCCGCGAGTGCCACCTGGAGGGACCCCGGCCCCACCCTTGGCTCCGCCCGGCCCACG GACCTGTTCGTCCCGCCCCTTGGCGGCTCCTACACTTCTGCTTTTCAGCCAGTTTTGCCT CGCAGCCCTAACTCGGGCATCCGAAGCTCCTAGTGGGCGCAGAAGCCAGCGGCTGCTGCC [SEO ID NO: 186] - FGF4

TGAGGTGAGGGCCGGAGGAGCAAGGGACAGAGGAGCAGGTGATGGAAATCC TGCAGCTTTAGGCTCCATTCTGCCATCTACATCCCAGCGCAGGGTGAAGCCTGAGAGCCC AAATGGCCAACTCCACAGGGCTGAACGCCTCAGAAGTCGCAGGCTCGTTGGGGTTGATCC TGCGCACGCCGGACTGCGCGCCCTCTACCTGGCGCACCTGTGCGTCGTGGACCTGC TGGCGGCCGCCTCCATCATGCCGCTGGGCCTGCTGGCCGCCGCCCGGGCTGGGCC GCGTGCGCCTGGGCCCGCGCCATGCCGCGCCGCTCGCTTCCTCTCCGCCGCTCTGCTGC CGCTGCGGCCAGGCTCGCGGCCGCCTGTGCTCGTGCTCACCGCCGTGTGGGCCGCGG GTCGCGCTGCCCTGAGGCCCCACGGCCGGCGCGGGTCCCGACTCCACTCGGACTCTC TGGATAGCCGCCTTTCCATCTTGCCGCCGCTCCGGCCTCGCCTGCCCGGGGGCAAGGCGG CGTGCCTGGCGCCGCAGCGCGGGCCGGGAAGCCGAAGCGGCTGTCACCTGGGTCGCCT ACTCGGCCTTCGCGGCTCACCCCTTCCTGTACGGGCTGCTGCAGCGCCCCGTGCGCTTGG ${\tt CACTGGGCCGCCTCTCTCGCCGTGCACTGCCTGGACCTGTGCGGGCCTGCACTCCGCAAG}$ $\tt CCTGGCACCCGCGGGCACTCTTGCAATGCCTCCAGAGACCCCCAGAGGGCCCTGCCGTAG$ GCCCTTCTGAGGCTCCAGAACAGACCCCCGAGTTGGCAGGAGGGCGGAGCCCCGCATACC AGGGGCCACCTGAGAGTTCTCTCTCTGAGCAGGAGAAAGGAGGGTGGTTTCCGTGGGGG CTCATCCAACCCCTGCACAGGTCACAGCAGGTGCCCTGCT

[SEO ID NO: 187] - GPR62

FIG 2GG

AGCAGGGCACCTGTGTGACCTGTGCAGGGGTTGGATGAGCCCCCACGGAAACCACCCTC CTTTCTCCTGCTCAGGAGAGAGACTCTCAGGTGGCCCCTGGTATGCGGGGCTCCGCCCT $\tt CCTGCCAACTCGGGGGTCTGTTCTGGAGCCTCAGAAGGGCCTACGGCAGGGCCCTCTGGG$ GGTCTCTGGAGGCATTGCAAGAGTGCCCGCGGGTGCCAGGCTTGCGGAGTGCAGGCCCGC ACAGGTCCAGGCAGTGCACGGCGAGAGAGGCGGCCCAGTGCCAAGCGCACGGGGCGCTGC AGCAGCCCGTACAGGAAGGGGTGAGCCGCGAAGGCCGAGTAGGCGACCCAGGTGACAGCC GCTTCGGCTTCCGCGGCCCGCGCTGCGGGCGCCAGGCACCGCGCAGCCATAAGGCAGCCAG CAGGCTGCAAATTGGCCCACGGCCAGCGCTGGGGCCAGGGCCGCCTTGCCCCCGGGCAGG CGAGGCCGGAGCGGCAAGATGGAAAGGCGGCTATCCAGAGAGTCCGAGTGGAGTCGG GACCCGCGCCGGCCGTGGGGGCCTCAGGGCAGCGCGACGCCCACCACGAAGATGCCG GGCGGCGTGCCGAGCAGGAGAGCGCGCCCAGCAGTCCCGCCGGCCCACACGGCGGTG AGCACGAGCACAGGCGGCGGCGGGGGCCGCGGCGGGTGCACGATGAGGCGGTAG CGTGCCAGGCCAAGTGCGGCCACCCCGAGCGTGCAGGCCGGCAGCAGAGCGGCGGAGAGG GCGGCCAGCAGCCCAGCGCATGATGGAGGCGCCCAGCAGGTCCACGACGCACAGG TGCGCCAGGTAGAGCGCGTCGCGCAGTCCCGGCGTGCGCAGCACCACCACCAGCAGCGCG CCGTTGCCCAGCAGTGCCCCCACCTCCACGACAGCTGCCAGGATCAACCCCAACGAGCCT GCGACTTCTGAGGCGTTCAGCCCTGTGGAGTTGGCCATTTGGGCTCTCAGGCTTCACCCT GCGCTGGGATGTAGATGGCAGAATGGAGCCTAAAGCTGCAGGATTTCCATCACCTGTCCT CTGCTCCTCTTGTCCCTTGCTCCTCCGGCCCCTCACCTCA

[SEQ ID NO: 188] - GPR62

 ${\tt CCGCGACCTTCGAGAACCCGCATGCTGTTCTCCACCAGGTCTCTCAGTCCTCCCTGCCCC}$ AATCCCCATGCCGGCCTCCGCGACCCTGTGATGCCTCCCTTCTTGCACAGGAGCAGTGAC GTGACTGGCAGGAGGCCGGGGGGGGGAACCCCCAAGCCCGGCGTCTGGGGCTGCGGGT CCGACCCGAGATCCGCCCTCCCTGCAAGCCCCGAGCCGCTGGCCAGGCCCGCTACTGCGC $\tt CCCACGGGGGGGGGGGCCGGGCCGGGGGGATCCCCGAAGCTACAGCGCC$ TTGCCTCCCTGCACGCTCCGCCCCCGGCCTCCGATTGGCTGTCGGGCCTAGAGCCCGC ${\tt CCAGAATTGGACCGTTCGCTTGTCGCTCGGGTCTGGCTCCACCCCCAGAGGGAGCCTAGA}$ ACCTGGTCGCAGTTTTTAGAGACTACCCTCACCCGTGGCCTGCGCCGAAGTTGGGCGGA GGACAGTGGGTGGCCAGGCCCTTCCGGGCCAGAACTCGGGACCCCTGCCAGCTACCCGTG CCAGGACAGACTCAAGCCCCCAAAACGCGGATGGATGTACAGAGGAGACTTGGGGAGAGC ACTGGACTGGGAGTCCTTGGGCCTGCACTGAACTCTGGCTGACTTTGTGACCTTGAAGAA ACTGCTTTTCCCTTCCTGAA

[SEQ ID NO: 189] - HEMK1

TTCAGGAAGGGAAAAGCAGTTTCTTCAAGGTCACAAAGTCAGCCAGAGTTCAGTGCAGGC GGGGCTTGAGTCTGTCCTGGCACGGGTAGCTGGCAGGGGTCCCGAGTTCTGGCCCGGAAG GGCCTGGCCACCCACTGTCCTCCGCCCAACTTCGGCGCAGGCCACGGGGTGAGGGTAGTC TCTAAAAACTGCGACCAGGTTCTAGGCTCCCTCTGGGGGTGGAGCCAGACCCGAGCGACA AGCGAACGGTCCAATTCTGGGCGGGCTCTAGGCCCGACAGCCAATCGGAGGCCGGGGGCC $\tt CGGAGCGTGCAGGGAGGCAAGGCGCTGTAGCTTCGGGGATCCCCCGAGGCTGCTCGGCCC$ GGCCCACCTCCGCCGTGGGTCCCGGCCCTACCCACCCTAGCTCAGGCCGGCAGAGCCAG CGCTCGCGGATGCGCTGGTGCGCAGTAGCGGGCCTGGCCAGCGGCTCGGGGCTTGCAGG GAGGGCGGATCTCGGGTCGGACCCGCAGCCCCAGACGCCGGGCTTGGGGGTTCCCCCCGC $\tt CCCGGCCTCCTGCCAGTCACTACCACCCCTAGCCTCTCCAACTGAGCTCGGCGCCGGGAG$ AGGATTAAGTAAGTGCTGAGGTCACTGCTCCTGTGCAAGAAGGGAGGCATCACAGGGTCG CGGAGGCGGCATGGGGATTGGGGCAGGGAGGACTGAGAGACCTGGTGGAGAACAGCATG CGGGTTCTCGAAGGTCGCGG

[SEQ ID NO: 190] - HEMK1

FIG 2HH

 $\tt CTGCAGCAGGACGTAAGCACAGTCATCGCTGCAAACTGCAAACTCGTAAGCACAGTCATC$ GCTGCAAACTGCAAACTCGTGCTCCGAGCGCTGCCCTCCCCTGTGGAGCGGAGGAGGGGGA GGCCTGGGGCCGCGGTGTGCGCCCCGCTCTGACCGCAGAGCCCCCTTCCCGAGGAAA GCGGCTGGCCCGGTCCCGGCTGGTGATCACGCGGGGCCCCTGTCTGCTTGGTGCGCAGGT GAGGGTCTGCCCTTCCGCTGCGCCCCGGACAGCCTGGAGGTGAGCACGCGCTGGGCCCTG GACCGCGAGCAGCGGGAGAAGTACGAGCTGGTGGCCGTGTGCACCGTGCACGCCGGCGCG CGCGAGGAGGTGGTGATGGTGCCCTTCCCGGTGACCGTGTACGACGAGGACGACTCGGCG CCCACCTTCCCGCGGGCGTCGACACCGCCAGCGCCGTGGTGGAGTTCAAGCGGAAGGAG CGGTCGGTTTAGTGTCCGTGTAGCCACCCAACCGTGTGGCCGACCATTCGCGCTTTCATT TGTCCTTCGCCTCCGTCTGCGCCGTCTGTCCTAGGGGGAGGGGAAGGGGGAGTCCTGCCA GCACCCAGCTGGGCCTTGCCTCGGGAGGCCAGGACCAGGACGAGGCCCGAGGGCTCGCGT GCCGGGAGGCACTCCCTCCCACCAGCAGTTAGCCCCCAACGGGAGGGCCCTTGAGTGAC CACGAGCAGAGCCGGGGATTGGAGAAGGACGGGAAGGCGGATCACCTCCGGCGCCCCG CCCCGCCTTCTCCGGCTCGCGCTGGTGGAGCGCGACCGCCACCTGCTGGGCCTCGGCCT TCCTGCAGCCGGCCCACCCAGCAGGGGCCGTGGGAGAGTGGGCGTGGGGACTGAGGTAGG TAGTACGTTGCCTTGTTCCGCTTCTCTGGG

[SEQ ID NO: 191] - RET

 $\tt CCCAGAGAAGCGGAACAAGGCAACGTACTACCTACCTCAGTCCCCACGCCCACTCTCCCA$ GTCCTTCTCCAATCCCCGGCTCTGCTCGTGGTCACTCAAGGGCCCTCCCGTTGGGGGCCTA $\tt CCCGCCTGCAGCGGCACAAGTATGCCCCAGACGCGAGCCCTCGGGCCTCGTCCTGGTCCT$ TGCCTCCGAGGCAAGGCCCAGCTGGGTGCTGGCAGGACTCCCCCTTCCCCTCCCCTAG GACAGACGCCCAGACGGAGGCGAAGGACAAATGAAAGCGCGAATGGTCGGCCACACGGT GGGTAGACCACAGCACGCGGGACAAGCACCTCCTTCCGCTTGAACTCCACCACGGCGCT GGCGGTGTCGACGCCCGCGGGGAAGGTGGGCGCCGAGTCGTCCTCGTCGTACACGGTCAC CGGGAAGGGCACCATCACCACCTCCTCGCGCGCGCGGCGTGCACGGTGCACACGGCCAC CAGCTCGTACTTCTCCCGCTGCTCGCGGTCCAGGGCCCAGCGCGTGCTCACCTCCAGGCT GTCCGGGGCGCAGCGGAAGGGCAGACCCTCACCTGCGCACCAAGCAGACAGGGGCCCCGC GTGATCACCAGCCGGGACCGGCCAGCCGCTTTCCTCGGGAAGGGGGCTCTGCGGTCAGA GCGGGGCGCACACCGCCGCGGCCCCAGGCCTCCCTCCTCCGCTCCACAGGGGAGGGCAG CGCTCGGAGCACGAGTTTGCAGTTTGCAGCGATGACTGTGCTTACGAGTTTGCAGTTTGC AGCGATGACTGTGCTTACGTCCTGCTGCAG

[SEQ ID NO: 192] - RET

GCGCCGACGGGGCGGTGGTAGGGGATGTACGGGTGTGTATATGCAGAGGTATGCCAGG CTCATTTAGGAGGGTTTGCAGGTCCAGAGTAAAGTCACTGAAGAGTGGAAGCGAGGAAGG AACAGGATGATTAGACCTCAGCTGCGGACCGCGGGGCTGGGACGATGCCTCCTGCCGGGG $\tt CTGCTGCTCCTGGTGCCCGTCCTCTGGGCCGGGGCTGAAAAGCTACATACCCAGCCC$ TCCTGCCCGCGGTCTGCCAGCCCACGCGCTGCCCGCGCTGCCCACCTGCGCGCTGGGG ACCACGCCGGTGTTCGACCTGTGCCGCTGTTGCCGCGTCTGCCCCGCGGCCGAGCGTGAA GTCTGCGGCGGGGCCAGGGCCAACCGTGCGCCCCGGGGCTGCAGTGCCTCCAGCCGCTG $\tt CGCCCGGGTTCCCCAGCACCTGCGGTTGCCCGACGCTGGGAGGGGCCGTGTGCGGCAGC$ CTGGGCAAGGTCCCGGCCGTGCCTGTGCAGTGGGGGAACTGCGGGGATACAGGTGAGCCG CGGGGGCGCGCCCTCGGAACACTTTCTAACTCTGGAGGAGCGTAAAGGAACAAGACCT CACTGAGACCGCACAGTTCGCGCCTGGTCCTCCTGCGTCATTTGCCTCCTGGATTCGACA CCTCTGTGTTCCTGATTTCC

[SEQ ID NO: 193] - HTRA4

FIG 2II

GGAAATCAGGAACACAGAGGTGTCGAATCCAGGAGGCAAATGACGCAGGAGGACCAGGCG CGAACTGTGCGGTCTCAGTGAGGTCTTGTTCCTTTACGCTCCTCCAGAGTTAGAAAGTGT TCCGAGGGCGCCCCCGCGGCTCACCTGTATCCCCGCAGTTCCCCCACTGCACAGGC ACGCCGGGACCTTGCCCAGGCGCGCGCGCGCGCGTTTTCGGCCCGGAGCGCGCACATG CTGGGGTAGGTGCGCTGCCGCACACGGCCCCTCCCAGCGTCGGGCAACCGCAG GTGCTGGGGAACCCGGGGCGCAGCGGCTGGAGGCACTGCAGCCCCGGGGCGCACGGTTGG CCCTGCGCCCGCGCAGACTTCACGCTCGGCCGCGGGCAGACGCGGCAACAGCGGCAC TGGCAGACCGCGGGCAGGAGGGCTGGGTATGTAGCTTTTCAGCCCCGGCCCAGAGGACG GGCACCAGGAGCAGCAGCCCCGGCAGGAGGCATCGTCCCAGCCCCGCGGTCCGCAGC TGAGGTCTAATCATCCTGTTCCTTCCTCGCTTCCACTCTTCAGTGACTTTACTCTGGACC CCAAACTTTAAGGGGCAGAGCCTGGCATACCTCTGCATATACACCCCGTACATCCCCTA CCACCGCCCCGTCGGCGC

[SEQ ID NO: 194] - HTRA4

TTGTCTTCTCCCTTCCGACCTCCCGTGGCCCCAGCGCGGCCAGCTCACAGTAGGTGCTCG GGCAGCGTTTCTTCAGGGACCTAGACGGCCTGGAGAGGAAGGGCCCCAGCCCAGCCCCC GGGCCTCTCACCTGGCTCTCGGGGCGCCCGGCTCGCACTTCCTCCCGCCGCCCCCCC TCCACATTCCTGCCCCGCGGGCCTGCCCCGCGCAGTCTGGGTCTCTGCGCCGCAGCCGC CCGCCCGCCCGCTCAGCGCCCGGGCTGACGGCGGCCCAGGCCGCGGGTGAGGAG GCGCCACCAGGCGTGCGGTCCGTCAAGGTGGTCCTGGTGGGCGACGGCGGCTGCGGGAAG ACGTCGCTGATGGTCTTCGCCGATGGGGCCTTCCCCGAGGTGAGTGCCCCGCGCCTC CGCCTCGCCCGGTTCCGCTCGCGCCCCGGGTGTACAGGTCCGTGCCGGAGCGGCCCAGG CTGTGCGCCTAACCCGGCCTCCGAGGGGTGTCCCAGCGGGCCTGGGGTCCAGGGCAGAG TTCTTCCGCCCCAGCCATTGGGAATGAAGGCCTCAGTGATGTTATCTGTAAAGCCGGAGG AGATCCTAAGACAGCACTTGGCCACACAATTCCGCTGAGGGCCTGAGAGCTTGGAAGCCA GACTGCCGAGGTTCAAATTATGGCTTTGCCTCTTATAGCTGTGTGCCCTTGGGTAAGTCC CCTAACCCTGCTGTGCCTGTG

[SEQ ID NO: 195] - RHOD

AGCCTCGCCTGGGGCTGATTGGCTCCCGAGGCCAGGGCTCTCCAAGCGGTTTATAAGAGT TGGGGCTGCCGGCCCTGCCCGCTCGCCCGCGCCCCAGGACCCAAAGCCGGGCTCC AAGTCGGCGCCCACGTCGAGGCTCCGCCGCAGCCTCCGGAGTTGGCCGCAGACAAGAAG GGGAGGGAGCGGAGAGGGAGGAGCTCCGAAGCGAGAGGGCCGATGCGCCGC GCCAGCAGAGACTACACCAAGTACCTGCGTGGCTCGGAGGAGATGGGCGGCGCCCCGGA GCCCGCACGAGGGCCCCTGCACGCCCCCCGCCGCCTGCGCCACCAGCCCCTGCC ${\tt GCCTCCGGTCCATGTTCGTGGCCCTCCTGGGGCTGGGGCTGGGCCAGGTTGTCTGCAGC}$ GTCGCCCTGTTCTTCTATTTCAGAGCGCAGGTGAGTGGCCACCTTCCCAGGGGATCGCGG CTGAGAGCGCCCATCTCCTTCCCCCGCACTTGGAAACTGAGTCTGGCGGCAGGGCTGGGC CACCCAGAGCTTGCATATTCCGGAAGGGAAAGTGACTCCAGAAGGGAGAGAGGAAGTGTT GAGTTTGGGGACAACCTGGCGCAGGGCTGTCGGGCGCACCCTGCTCTCTCCCGCCCACG CACCCAGCTTCTCGGTGCTCTGGGGGGGGGACTCCCCTGGCCGGACGATGGGTTTGAATC TCACCCCGTCCCTTCGCTGGGAAACAACACTGGCCTCTCACCTTTTCTGGTAGTGATTGC ATACTTTTTCTCCCTGTCATTTCTCACTTGAAGTTAAGAATCAACTTCTGTTCACGTAGG AAAAAAGATGAGCGCCTTCACTTGGGCATCTACCTTTCCCTTCCCGCCCACCACCGGCG GGTTTCGGTTCCTGCGCCTGGCTGCTCTGCAGGTGTGCTGGGGGCCACGGTGCTGGAGGGC TGCGCGGAGCGGGAGGTCGCGGTGCTCGTGCCCAGGTCGCCCAATGGGTGGCCAGAATGA CACGGCGCGACCAGAGAGGCGCGGGCTCGGGATGGGGGCTCTGCGGCTGTGGCGCTGTCC TGTGGGGGTGAAGGAAGAGGGACAGCCCCACGTGCCTAGGGATGTGGGCGGAGGAAG AAAGATGAAGAGGTTTTTTGCACGACGGCTAGGAACTGCAG

[SEQ ID NO: 196] - TNFSF11

FIG 2JJ

GCAATTTATAGATGAGAGCGTGGACGGCAGAGAGCATTGTGTATGTTGAAGTCTCTGCGATATGGGGT GTCCCTGCTGCCCCGCTCCAGCCTTTCACTTCTGACCTCCTTCTGGCTCTTACGCTACAGGATCC AAAACTACTCGGAAGACTTGCCGCGGGCGGTGATTGACGACGCCTTTGCCCGCGCCTTCGCACTGTGG $\tt AGCGCGGTGACGCCGCTCACCTTCACTCGCGTGTACAGCCGGGACGCAGACATCGTCATCCAGTTTGG$ TGTCGCGGGTGAGAACGTGAGGAGGGAAAATCCAAGAGACCTGGGCGGGGTCAGGGAAGGGAGGACCA AGCCCGCACTTATTTCGGAGCCCTTGCCTTGGGCAGCGCACAATCTGCGCAGCAGTACTCGGCTAACC TGGCACACGCCTTTCCTCCTGGCCCCGGCATTCAGGGAGACGCCCATTTCGACGATGACGAGTTGTGG TCCCTGGGCAAGGGCGTCGGTGAGATTCTGAGTCCTCCTGGCCCCTGATTCCCTTCATTCTCCCACTCATCACCCCGCCGCCCTAACTCCGGTCCCCCCCTCCTCCTGCAGTGGTTCCAACTCGGTTTGGAAACGC GTCGCTCCGACGGCTTGCCCTGGTGCAGTACCACGGCCAACTACGACACCGACGACCGGTTTGGCTTC TGCCCCAGCGAGAGTGAGGGGGGCTCGCCGAGGGCTGGGGGGCCCCACCACCCTTGATGGTCCTG GGTTCTAATTCCAGCTCTGCCACTAGTGCTGTGGGCCTGCAATTCACCCTCCCGCACTCTGGGCCCA ATTGGTCCTCAGGACGGTGACTCCGCCCACCTACACCACATTTCCACCACTATCCCTGACTTCCA ATGGCCCGCCCCAGCCACTAAGGTTCGGCCTTTTCTGCCCAGCTGGCCGCCTCTTCCTTGGTCTGGT GTCCCAGGCACCGCCCACGGGTCTAGCCTCTTCTCAGGAGTGCTCTACAGCGCCCCCTAGGCCACCAA GCCTTGGGTCTCCCAGCTGACTCGACGGTGATGGGGGGGCAACTCGGCGGGGGGAGCTGTGCGTCTTCC CCTTCACTTTCCTGGGTAAGGAGTACTCGACCTGTACCAGCGAGGGCCGCGGAGATGGGCGCCTCTGG TGCGCTACCACCTCGAACTTTGACAGCGACAAGAAGTGGGGCTTCTGCCCGGACCAAGGTAGGCGTGG CCGGCGCTCACGTCTCAGGCTCCCTCTCCCTCCAGGATACAGTTTGTTCCTCGTGGCGGCGCATGAGT TCGGCCACGCGCTGGGCTTAGATCATTCCTCAGTGCCGGAGGCGCTCATGTACCCTATGTACCGCTTC AAGCCAGTCTACTCTGGGCATGGTGGCTCACGCCTCTAATCCCAGGGCTTTGGGAGACCCAAGGCGGG AGGATTGCTTAAGCCCAGGAGTTCCAGACCAGCCTCGGCAACATAGCCAGACTCCCATCTCTACAAAA AATAAATGAGCAAGGCGTGAAGGCACATGTCTGTAGTCCTAGCTACTCTGGAGGCTGAGGTGGGAGGA TCTCTTGAGCCCAGGAGTTCGAGGCTGTAGTGAGCTATGCACCACTGCATTCCATCCTGGGCCA AGAGGTATGCAGGAATAGGAAGAGTCTCACCCCGTGTCTCTTTTTAGGTCCTCGCCCTGAACCTGAGC CACGGCCTCCAACCACCACCACCGCAGCCCACGGCTCCCCCGACGGTCTGCCCCACCGGACCCCC ACATCTTCGACGCCATCGCGGAGATTGGGAACCAGCTGTATTTGTTCAAGGATGGGTGAGGAGGCGGG GTTGTGTGGATGCGGGAGGGGCTTTGCGGAGGGGCTGCCCTTCCCGCCCACTGGCCCTGTGT CCGCCCGGTCAATCCCCATCAGTCAAGGAGGCTCAAGAGACCATCGATAACCCACGAAACGTCTTGTG CGTTTTAGAAAAATACGCCCCTGGCGGACGCAGTTTAGCAAACGTAGGGGCGGCTGAGTTTCTGCCCCCTCCTCTCCACGCCCTCGCGTCGCTCTACCCAGCGCCTCTGCCCCTGGGTTGCAGGGACTGCGGGCA CGCGGGCTAGGAAAGGCCTCGCCGGAATCTCCCTCCTCGCGTTCTAGGAGTACGTGCTCCCTCTGCGC TGGGCCCGAGGCGTCTGGACAAGCTGGGCCTGGGAGCCGACGTGGCCCAGGTGACCGGGGCCCTCCGG $\tt CCCGCAGGTTCGACGTGAAGGCGCAGATGGTGGATCCCCGGAGCGCCAGCGAGGTGGACCGGATGTTC$ AATGGAAACAAATGCCCCAGCACAGACAAGATCCCAGCAGAGGCCAGAGGCCTTCTCCAGGTCATTTAG GAAGTCAGGGATGCAAC

[SEQ ID NO: 197] - MMP9

FIG 2KK

CAGGAACTTTCGAGATGAGGTGCCTTTCCCAAGGTGACACTAAGTGGAGGAGCCCAGCCA GAGTCCAGGGGTCCTTACACAACCTTCGGTGGTCTCTCTTTACCTGTGAAGCTGCAGCCT GCTTCCCAGCTCGGGGGCGTGTACAGGAGACTGGACCTGGGGCAGCCTCAGAATGCCTGG $\tt CTGCCTGGAGCTCTCCTCGCGTGTCCAGGCGGCCTGCTTGGTCTCCCTCTCTCCCTCT$ ${\tt TAGGTGCCGGGGCACCCGGTGCAGGGTGGGCACGGCCTGCCACCAGCCTCAGGC}$ GCTGGGAGAAGCGCAGGTTCTTCTGGATAACCGAAGACGTCAAAACAGGCTGGGGCAA AGTGGTCAGAGCAGATGACCGAGCGGTCATTGCCTCCGTACCAGTCGGCGCGGCAACCCC GCACGAAGCGGTCCCAGAGCAGCCGCACGGCCCGGTCCTTGGGAAAGCGGAACAGCGACT TCCCAGACTTGGTGTTTGCCGCAGTGGGCGGCCACACAACGGGCCGGCATGGCGGCCG TCTTCGGTGCGCGGGACCCGGGTTCCCTGGACCTTCGCCCTTGGGCACGCTCCTCGCAGC GGCCTCGGCGAGGCAAGTCCTCCCCTCCTCACCTGTCCACTCCGGGTCGGGATTGTTTCC TTCCCTACCTCTGGTCACCGGAAGTGGCGATCTGGGGCCCCCAATGGGAGGGCTCTTTGA TATCTTCCTCCTCCTCCTGCGCTGCTCCCCAGGAGCCAGTGGACACAAGCAGAGGG ATACAAATTTCGCGCGGGCAG

[SEQ ID NO: 198] - LRRC49

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MATERIALS AND METHOD FOR ASSAYING FOR METHYLATION OF CPG ISLANDS ASSOCIATED WITH GENES IN THE EVALUATION OF CANCER

CROSS-REFERENCE TO RELATED APPLICATIONS

This patent application is a divisional of U.S. patent application Ser. No. 12/115,674, filed on May 6, 2008, now abandoned, which is a continuation of International Patent Application No. PCT/US2006/060685, filed Nov. 8, 2006, designating the United States, which claims the benefit of U.S. Provisional Patent Application No. 60/734,577, filed Nov. 8, 2005, which are incorporated by reference herein in 15 their entireties.

INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ELECTRONICALLY

Incorporated by reference in its entirety herein is a computer-readable nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: One 214,875 Byte ASCII (Text) file named "702375_ST25.TXT," created on May 2, 2008.

BACKGROUND OF THE INVENTION

Phosphate linked cytosine-guanine (CpG) dinucleotides are statistically underrepresented in the genomes of higher 30 eukaryotes, including mammals. The dinucleotide is reportedly found at only 5-10% of its predicted frequency. The majority of CpG dinucleotides that do remain in the human genome are normally located within repetitive sequences that are characterized by low gene expression levels and exhibit 35 methylation at the cytosine residues.

CpG islands, on the other hand, represent genomic sequences that contain clusters of CpG dinucleotide. CpG islands may be associated with the promoter region or 5' end of coding sequences or may be present within introns or in 40 genomic regions that are not known to be associated with coding sequences. They may be unmethylated or methylated in normal tissues and the methylation pattern may be used to control tissue specific expression and the expression of imprinted genes. Methylation of CpG islands within pro- 45 moter regions can result in the downregulation or silencing of the associated gene. An increase in methylation of normally unmethylated islands is observed in aging tissues even as the overall methylcytosine content of the DNA is reduced. The aberrant methylation pattern is more pronounced in cancer 50 cells with increased methylation or hypermethylation detected in various cancer tissues. CpG islands may be methylated to varying densities within the same tissue. Thus, aberrant methylation of cytosines within CpG islands can be a primary epigenetic event that acts to suppress the expression 55 of genes involved in critical cellular processes, such as DNA damage repair, hormone response, cell-cycle control, and tumor-cell adhesion/metastasis, leading to tumor initiation, progression and metastasis (Li et al., Biochim. Biophys. Acta, 1704: 87-102 (2004)). It has been proposed that a unique 60 profile of promoter hypermethylation exists for each human cancer in which some gene changes are shared and other gene changes are cancer-type specific (Esteller et al., Cancer Res., 61: 3225-3229 (2001)). Given that aberrant methylation represents new information not normally present in genomic 65 DNA and that aberrant methylation is a common DNA modification and affects a large number of genomic targets, it is

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feasible to develop diagnostic and prognostic tests based on information obtained from multiple target CpGs. Such tests may be based on CpGs that are aberrantly hypermethylated or hypomethylated in the diseased tissues. They may also be based on changes in methylation density in CpG islands as long as the changes corrolate with the presence of cancer.

Prostate cancer, for example, which is the most common malignancy and the second leading cause of death among men in the U.S. (Li et al. (2004), supra), has been found to be associated with the methylation of CpG islands in the promoters of over 30 genes, in particular the CpG island of the glutathione S-transferase P1 (GSTP1) gene. GSTP1 methylation has been detected in over 50% of DNA recovered from urine and plasma of prostate cancer patients (Goessl et al., Ann. N.Y. Acad. Sci., 945: 51-58 (2001); Cairns et al., Clin. Cancer Res., 7: 2727-2730 (2001); Jeronimo et al., Urology, 60: 1131-1135 (2002); and Gonzalgo et al., Clin. Cancer Res., 9: 2673-2677 (2003)). However, if diagnosis of prostate cancer relied solely on the detection of the methylation of the 20 CpG island in the GSTP1 gene, the theoretical limit of the sensitivity of such a test would only be approximately 90%. GSTP1 is also methylated in prostatic intraepithelial lesions (PIN) which may lead to a false positive diagnosis. Some CpG islands are methylated in prostate cancer and other diseases of the prostate, such as benign prostatic hyperplasia (BPH). They may even exhibit some degree of methylation in normal aging prostates. Such markers may not be suitable individually for prostate cancer diagnosis. Therefore, a panel of markers is required to achieve the sensitivity and specificity needed for a clinical test.

The prostate-specific antigen or PSA test continues to be widely used in the early detection of prostate cancer. While the PSA test has resulted in the majority of prostate cancer cases being diagnosed in asymptomatic men (Mettlin et al., Cancer, 83(8): 1679-1684 (1998a); Mettlin et al., Cancer, 82(2): 249-251 (1998b); Humphrey et al., J. Urol., 155: 816-820 (1996); and Grossfeld et al., *Epidemiol. Rev.*, 23(1): 173-180 (2001)), the PSA test suffers from poor specificity, which can be as low as 33% when a PSA cut-off level of 2.6 ng/ml is used (Thompson et al., N. Engl. J. Med., 350: 2239-2246 (2004)), even though the sensitivity can be as high as 83%. The poor specificity of the PSA test is a direct result of increased secretion of PSA in other diseases of the prostate, such as BPH and prostatitis. Thus, an elevated PSA level indicates the need for additional screening in the form of needle biopsy. Ultimately, the results of needle biopsies lead to the diagnoses of prostate cancer.

Over 1 million needle biopsies of prostates are performed each year at a cost of about \$1,500 each and much discomfort to the patient. However, less than 200,000 of these result in a diagnosis of prostate cancer. Therefore, the majority of needle biopsies are being performed needlessly.

In view of the above, there is a need for non-invasive methods of diagnosing and prognosticating cancer, such as prostate cancer, that reduce the cost and suffering associated with currently available cancer screening methods. It is an object of the invention to provide materials and methods for non-invasive diagnosis and prognosis of cancer, such as prostate cancer. This and other objects and advantages, as well as additional inventive features, will become apparent from the detailed description provided herein.

BRIEF SUMMARY OF THE INVENTION

The invention provides materials and methods for evaluating cancer. Methods of evaluating can include methods of diagnosing and prognosticating cancer as well as methods of

assessing the efficacy of cancer treatment. Generally, the methods provided involve assaying for methylation of CpG islands associated with specific genes. The invention also provides pairs of isolated or purified primers that can be used in the methods of the invention, for example, to amplify 5 and/or detect the methylation state of the CpG islands associated with specific genes. The invention also provides kits comprising one or more pairs of primers useful in the disclosed methods.

The invention provides methods of diagnosing cancer by 10 assaying for one or more methylated CpG islands that are indicative of cancer. Generally, the method comprises providing a biological sample from a subject in need of cancer diagnosis and assaying the sample for methylation of one or more CpG islands associated with at least one gene selected 15 from the group consisting of: neuregulin cell-surface ligand (NRG1), adrenergic B3 receptor (ADRB3), glycosylphosphatidyl-inositol cell-surface receptor (GFRA2), kinesin family member 13B (KIF13B), RET proto-oncogene (RET), G-protein-coupled protein receptor 147 (GPR147), neuroge- 20 nin 3 transcription factor (NEUROG3), paladin (predicted protein tyrosine phosphatase) (PALD), methyltransferase family member 1 (HEMK1), fibroblast growth factor 4 oncogene (FGF4), 5-hydroxytryptamine (serotonin) receptor 1A (HTR1A), ring finger protein 180 (LOG 285671 or RNF180), 25 EGFR-co-amplified and overexpressed (DKFZP564K0822 or ECOP), zinc finger protein 596 (ZNF596), similar to 7 transmembrane helix receptor (LOC441320), L-threonine dehydrogenase (TDH), hypothetical protein FLJ36980 (FLJ36980), fibroblast growth factor receptor 20 (FGF20), 30 EF-hand domain family member 2A (LOC286097 or EFHA2), N-acylsphingosine amidohydrolase (acid ceraminase) 1 (ASAH1), nodal homolog (TGF-β signaling pathway) (NODAL), hypothetical protein similar to zinc finger protein 532 (LOC399783), transcription factor LIM home- 35 odomain (ISL2) Kinesin family member C2 (KIFC2), chromosome 20 open reading frame 23 (Kinesin-like motor protein) (C20orf23), GDNF family receptor alpha 1 (GFRA1), Glutathione peroxidase 7 (GPX7), Dickkopf homolog 2 (MMP9), tumor necrosis factor superfamily member 11 (TN-FSF11), ras homolog gene family member D (RHOD), and leucine rich repeat containing 49 (LRRC49).

The invention also provides a method of diagnosing prostate cancer in a male mammal by assaying for one or more 45 methylated CpG islands that are indicative of prostate cancer. The method can include providing a biological sample from a subject in need of cancer diagnosis and assaying the sample for methylation of a CpG island associated with at least one gene selected from the group consisting of: NRG1, ADRB3, 50 GFRA2, KIF13B, RET, GPR147, NEUROG3, PALD, HEMK1, FGF4, HTR1A, RNF180, ECOP, ZNF596, LOC441320, TDH, FLJ36980, EFHA2, ASAH1, NODAL, LOC399783, ISL2, MMP9, TNFSF11, RHOD, LRRC49, Kinesin family member C2 (KIFC2), chromosome 20 open 55 reading frame 23 (Kinesin-like motor protein) (C20orf23), GDNF family receptor alpha 1 (GFRA1), Glutathione peroxidase 7 (GPX7), Dickkopf homolog 2 (DKK2), netrin 1 (NTN1), Ras association (Ra1GDS/AF-6) domain family 5 (RASSF5), and HtrA serine peptidase 4 (HTRA4). Option- 60 ally, the method of diagnosing prostate cancer can also include assaying for methylation of one or more CpG island associated with at least one gene that is known to be methylated in prostate cancer but is known not to be detectably methylated or is methylated at a lower level (e.g., about 50% 65 or less, about 40% or less, 30% or less, about 20% or less, or about 10% or less) in BPH.

The invention also provides methods of prognosticating cancer by assaying for the methylation of one or more genes that are indicative of the grade or stage of the cancer, and/or the length of disease-free survival following treatment for cancer. Generally, the method comprises providing a biological sample from a subject in need of cancer prognosis and assaying the sample for methylation of a CpG island associated with at least one gene selected from the group consisting of: NRG1, ADRB3, GFRA2, KIF13B, RET, GPR147, NEU-ROG3, PALD, HEMK1, FGF4, HTR1A, RNF180, DKFZP5640822, ZNF596, LOC441320, TDH, FLJ36980, FGF20, EFHA2, ASAH1, NODAL, LOC399783, ISL2, KIFC2, C20orf23, GFRA1, GPX7, DKK2, NTN1, MMP9, TNFSF11, RHOD and LRRC49.

Further provided by the invention is a method of prognosticating prostate cancer in a male mammal by assaying for one or more methylated CpG islands that are indicative of the grade or stage of prostate cancer, and/or the length of diseasefree survival following treatment of prostate cancer. The method comprises providing a biological sample from the male mammal and assaying the sample for methylation of a CpG island associated with at least one of the following genes: NRG1, ADRB3, GFRA2, KIF13B, RET, GPR147, NEUROG3, PALD, HEMK1, FGF4, GPR62, HTR1A, RNF180, DKFZP5640822, ZNF596, LOC441320, TDH, FLJ36980, FGF20, EFHA2, ASAH1, NODAL, LOC399783, ISL2, KIFC2, C20orf23, GFRA1, GPX7, DKK2, NTN1, RASSF5, HTRA4, MMP9, TNFSF11, RHOD or LRRC49. Optionally, the method of prognosticating prostate cancer can also include assaying the biological sample for methylation of a CpG island associated with at least one gene that is known to be methylated in prostate cancer but is known not to be detectably methylated or is methylated at a lower level (e.g., about 50% or less, about 40% or less, 30% or less, about 20% or less, or about 10% or less) in BPH. Methylation of the CpG islands associated with the genes is indicative of the grade or stage of the cancer, and/or the length of disease-free survival following treatment.

Furthermore, the invention provides methods of assessing (DKK2), netrin 1 (NTN1), matrix metallopeptidase 9 40 the efficacy of treatment of cancer by assaying for the reduced methylation of CpG islands that indicates efficacy of treatment. Generally, the method comprises providing a first and a second biological sample from a subject in need of assessing the efficacy of treatment of cancer and assaying the samples for a change in methylation level of a CpG island associated with at least one gene selected from the group consisting of: NRG1, ADRB3, GFRA2, KIF13B, RET, GPR147, NEU-ROG3, PALD, HEMK1, FGF4, HTR1A, RNF180, DKFZP5640822, ZNF596, LOC441320, TDH, FLJ36980, FGF20, EFHA2, ASAH1, NODAL, LOC399783, ISL2, KIFC2, C20orf23, GFRA1, GPX7, DKK2, NTN1, MMP9, TNFSF11, RHOD and LRRC49. The first biological sample is taken before the second biological sample, and the second biological sample is taken during or after a course of treatment. A decrease or absence of methylation of the assayed one or more CpG islands in the second sample (i.e., following the course of treatment) indicates that the treatment is effective. Alternatively, the maintenance or increase of methylation in the assayed CpG islands in the second sample can indicate a reduction or absence of treatment efficacy.

Also provided is a method of assessing the efficacy of treatment of prostate cancer in a male mammal by assaying biological samples, which are taken from the male mammal periodically during the course of treatment, for methylation of a CpG island and wherein a decrease or absence of methylation of the CpG islands following the course of treatment indicates that the treatment is effective. The method com5

prises (a) providing a first and a second biological sample from a subject undergoing a course of cancer treatment, wherein the first sample is taken at an earlier time than the second sample, and the second sample is taken during or following a course of treatment and (b) assaying the samples 5 for methylation of a CpG island associated with at least one gene selected from the group consisting of: NRG1, ADRB3, GFRA2, KIF13B, RET, GPR147, NEUROG3, PALD, HEMK1, FGF4, HTR1A, RNF180, DKFZP5640822, ZNF596, LOC441320, TDH, FLJ36980, FGF20, EFHA2, ASAH1, NODAL, LOC399783, ISL2, KIFC2, C20orf23, GFRA1, GPX7, DKK2, NTN1, RASSF5, HTRA4, MMP9, TNFSF11, RHOD and LRRC49. Optionally, this method can also include assaying the biological sample for methylation of a CpG island associated with at least one gene that is known to be methylated in prostate cancer but is known not to be detectably methylated or is methylated at a lower level (e.g. about 50% or less, about 40% or less, 30% or less, about 20% or less, or about 10% or less in BPH.

In preferred embodiments, the aforementioned methods of diagnosing, prognosticating and assessing the efficacy of treatment of cancer can further include assaying the biological sample for methylation of multiple CpG islands, for example, CpG islands associated with two, three, four, five, 25 six, seven, eight, nine, ten, eleven, or more genes.

Additionally, the invention provides a terminator-coupled linear amplification method of determining the methylation status of a CpG island. Generally, the method includes providing a DNA sample for terminator-coupled linear amplification and then incubating the DNA sample under deaminating conditions to thereby produce a deaminated DNA sample. Optionally, the deaminated DNA sample can be purified. The deaminated sample is used as template to amplify a target sequence or target sequences that include one or more CpG islands or portions of one or more CpG islands thereby producing one or more amplified target sequences. Optionally, the one or more amplified target sequences are purified. One early amplified in the presence of a primer and a dideoxynucleotide to generate one or more fragments of different lengths, wherein each length corresponds to the distance in bases from the 5' end of the primer to the position where the dideoxynucleotide is incorporated. Optionally, the one or 45 more fragments is purified. The one or more fragments are analyzed to determine their lengths. The lengths of the fragments can be used to determine the methylation status of methylated cytosines within the one or more amplified target sequences.

The invention also provides pairs of primers suitable for amplifying a CpG-island associated with genes described herein. Primers can include isolated or purified nucleic acid molecules suitable for amplifying a CpG island containing target sequence. Target sequences can include genomic 55 sequence that has been fully methylated and fully deaminated such as those in SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, 60 SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID 65 NO: 36, SEQ ID NO: SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42,

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SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, and SEO ID NO: 54.

Exemplary primer pairs include SEQ ID NOs: 55 and 56, SEO ID NOs: 57 and 58, SEO ID NOs: 59 and 60, SEO ID NOs: 61 AND 62, SEQ ID NOs: 63 and 64, SEQ ID NOs: 65 and 66, SEQ ID NOs: 67 and 68, SEQ ID NOs: 69 and 70, SEQ ID NOs: 71 and 72, SEQ ID NOs: 73 and 74, SEQ ID NOs: 77 and 78, SEQ ID NOs: 79 and 80, SEQ ID NOs: 81 and 82, SEQ ID NOs: 83 and 84, SEQ ID NOs: 87 and 88, SEQ ID NOs: 89 and 90, SEQ ID NOs: 91 and 92, SEQ ID NOs: 93 and 94, SEQ ID NOs: 95 and 96, SEQ ID NOs: 97 and 98, SEQ ID NOs: 103 and 104, SEQ ID NOs: 105 and 106, SEQ ID NOs: 107 and 108, SEQ ID NOs: 109 and 110, SEQ ID NOs: 111 and 112, SEQ ID NOs: 113 and 114, SEQ ID NOs: 115 and 116, SEQ ID NOs: 117 and 118, SEQ ID NOs: 199 and 200, SEQ ID NOs: 201 and 202, SEQ ID NOs: 203 and 204, SEQ ID NOs: 205 and 206, SEQ ID NOs: 207 and 208, SEQ ID NOs: 209 and 210, SEQ ID NOs: 211 and 212, SEQ ID NOs: 213 and 214, SEQ ID NOs: 215 and 216, SEQ ID NOs: 217 and 218, SEQ ID NOs: 219 and 220, SEQ ID NOs: 221 and 222, SEQ ID NOs: 224 and 225, SEQ ID NOs: 227 and 228, SEQ ID NOs: 227 and 228, SEQ ID NOs:

Also provided are kits that include one or more of the aforementioned pairs of primers.

BRIEF DESCRIPTION OF THE FIGURES

FIGS. 1A-1DD set forth the nucleotide sequences for SEQ ID NOs: 1-54. Sequences are presented in accordance with convention from left to right and top to bottom.

FIGS. 2A-2KK set forth the nucleotide sequences for SEQ ID NOs: 119-198. Sequences are presented in accordance with convention from left to right and top to bottom.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides a method of diagnosing cancer by or more sequences in the amplified target sequences are lin- 40 assaying for the methylation of one or more CpG islands that are indicative of cancer. Cancer can include, for example, lung, liver, pancreas, head and neck, throat, thyroid, esophagus, brain, ovarian, kidney, skin, colorectal, and hematopoeietic (e.g., lymphomas and leukemic) cancer. Generally, the method comprises providing a biological sample from a subject in need of cancer diagnosis and assaying the sample for methylation of a CpG island associated with at least one gene selected from the group consisting of: NRG1, ADRB3, GFRA2, KIF13B, RET, GPR147, NEUROG3, PALD, HEMK1, FGF4, HTR1A, RNF180, DKFZP5640822, ZNF596, LOC441320, TDH, FLJ36980, FGF20, EFHA2, ASAH1, NODAL, LOC399783, ISL2, KIFC2, C20orf23, GFRA1, GPX7, DKK2, NTN1, MMP9, TNFSF11, RHOD or LRRC49. In preferred embodiments, the method can include assaying for methylation of CpG islands associated with two, three, four, five, six, seven, eight, nine, ten, eleven, or more of the foregoing genes. Methylation of the CpG islands associated with these genes is indicative of cancer.

The invention further provides a method of diagnosing prostate cancer by assaying for the methylation of one or more CpG islands that are indicative of prostate cancer in a male mammal. In one embodiment, the method comprises providing a biological sample from a male mammal in need of cancer diagnosis and assaying the sample for methylation of a CpG island associated with at least one gene selected from the group consisting of: NRG1, ADRB3, GFRA2, KIF13B, RET, GPR147, NEUROG3, PALD, HEMK1, FGF4,

HTR1A, RNF180, DKFZP5640822, ZNF596, LOC441320, TDH, FLJ36980, FGF20, EFHA2, ASAH1, NODAL, LOC399783, KIFC2, C20orf23, GFRA1, GPX7, DKK2, NTN1, HTRA4, MMP9, TNFSF11, RHOD and LRRC49. For example, the method of diagnosing prostate cancer 5 includes assaying the biological sample for methylation of a CpG island associated with NRG1, KIF13B, or both. In another example, the method includes assaying for methylation of a CpG island associated with at least one gene selected from the group consisting of: TDH, ASAH1, FGF20, 10 HEMK1, PALD NEUROG, EFHA2, KIFC2, GFRA1, DKK2, TNFSF11, NTN1, and RHOD. In preferred embodiments, the method of diagnosing prostate cancer can include assaying for methylation of CpG islands associated with two, three, four, five, six, seven, eight, nine, ten, eleven, or more of 15 the foregoing genes. Methylation of the CpG islands associated with these genes is indicative of cancer.

The foregoing method of diagnosing prostate cancer can optionally include, in combination with assaying for methylation of CpG islands associated with the foregoing genes, 20 further assaying the biological sample for methylation of a CpG island associated with at least one gene that is known to be (i) methylated in prostate cancer and (ii) not detectably methylated or methylated at a lower level (e.g., about 50% or less, about 40% or less, about 30% or less, about 20% or less, 25 or less than about 10%) in BPH. In this regard, when the method includes assaying for at least one CpG island that is known to be methylated in prostate cancer but is known not to be detectably methylated or methylated at a lower level in BPH, the method preferably includes assaying the biological 30 sample for methylation of CpG islands associated with at least three different genes. Examples of CpG islands known to be methylated in prostate cancer but not detectably methylated or methylated at a lower level in BPH include CpG (GSTP1), glutathione peroxidase 3 (GPX3), glutathione S-transferase M1 (GSTM1), glutathione S-transferase M4 (GSTM4), Cub and Sushi multiple domains1 (CSMD1), tumor necrosis factor receptor superfamily member 10A (TNFRSF10A) tumor necrosis factor receptor superfamily 40 member 10B (TNFRSF10B), tumor necrosis factor receptor superfamily member 10C (TNFRSF10C), tumor necrosis factor receptor superfamily 10D (TNFRSF10D), secreted frizzled-related protein 1 (SFRP1), secreted frizzled-related protein 2 (SFRP2), dickkopf homolog 3 (DKK3), prostaglan- 45 din-endoperoxide synthase 2 (PTGS2), cyclin-dependent kinase inhibitor 1C (CDKN1C/p57), Ras association (Ra1GDS/AF-6) domain family 1 (RASSF1), and G-protein coupled receptor 62 (GPR62).

The invention also provides a method of prognosticating 50 cancer by assaying for the methylation of one or more genes that are indicative of the grade or stage of the cancer, and/or the length of disease-free survival following treatment for cancer. Generally, the method comprises providing a biological sample from a subject in need of cancer prognosis and 55 assaying the sample for methylation of a CpG island associated with at least one gene selected from the group consisting of: NRG1, ADRB3, GFRA2, KIF13B, RET, GPR147, NEU-ROG3, PALD, HEMK1, FGF4, HTR1A, RNF180, DKFZP5640822, ZNF596, LOC441320, TDH, F1136980, 60 FGF20, EFHA2, ASAH1, NODAL, LOC399783, ISL2, KIFC2, C20orf23, GFRA1, GPX7, DKK2, NTN1, MMP9, TNFSF11, RHOD and LRRC49. In preferred embodiments, the method can include assaying for methylation of CpG islands associated with two, three, four, five, six, seven, eight, 65 nine, ten, eleven, or more of the foregoing genes. Methylation of the CpG islands associated with these genes is indicative of

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the grade or stage of the cancer, and/or the length of diseasefree survival following treatment for cancer.

The invention also provides a method of prognosticating prostate cancer in a male mammal by assaying for the methylation of one or more CpG islands that are indicative of the grade or stage of the prostate cancer, and/or the length of disease-free survival following treatment for prostate cancer. In one embodiment, the method comprises assaying a biological sample from the male mammal for methylation of a CpG island associated with at least one of the following genes: NRG1, ADRB3, GFRA2, KIF13B, RET, GPR147, NEUROG3, PALD, HEMK1, FGF4, HTRIA, RNF180, DKFZP5640822, ZNF596, LOC441320, TDH, F1136980, FGF20, EFHA2, ASAH1, NODAL, LOC399783, or ISL2. In addition to or instead of the foregoing, the method can include assaying the biological sample for methylation of a CpG island associated with at least one of the following genes: KIFC2, C20orf23, GFRA1, GPX7, DKK2, NTN1, RASSF5, HTRA4, MMP9, TNFSF11, RHOD or LRRC49. For example, the method of diagnosing prostate cancer includes assaying the biological sample for methylation of a CpG island associated with NRG1, KIF13B, or both. In another example, the method includes assaying for at least one of the following genes: TDH, ASAH1, FGF20, HEMK1, PALD NEUROG, EFHA2, KIFC2, GFRA1, DKK2, TNFSF11, NTN1, or RHOD. In preferred embodiments, the method of diagnosing prostate can include assaying for methylation of CpG islands associated with two, three, four, five, six, seven, eight, nine, ten, eleven, or more of the foregoing genes. Methylation of the CpG islands associated with these genes is indicative of the grade or stage of prostate cancer, and/or the length of disease-free survival following treatment for prostate cancer.

The foregoing method of prognosticating prostate cancer islands associated with glutathione S-transferase P1 35 can optionally include, in combination with assaying for methylation of CpG islands associated with the foregoing genes, further assaying the biological sample for methylation of a CpG island associated with at least one gene that is known to be (i) methylated in prostate cancer and (ii) not detectably methylated or methylated at a lower level (e.g., about 50% or less, about 40% or less, about 30% or less, about 20% or less, or less than about 10%) in BPH. Percent methylation level in BPH refers to the percent of patients that exhibit some detectable level of methylation at that locus. In this regard, when the method includes assaying for methylation of at least one CpG island that is known to be methylated in prostate cancer but is known not to be detectably methylated or is methylated at a lower level in BPH, the method preferably includes assaying the biological sample for methylation of CpG islands associated with at least three different genes. Examples of CpG islands known to be methylated in prostate cancer but not detectably methylated or methylated at a lower level in BPH include CpG islands associated with GSTP1, GPX3, GSTM1, GSTM4, CSMD1, TNFRSF10A, TNFRSF10B, TNFRSF10C, TNFRSF10D, SFRP1, SFRP2, DKK3, PTGS2, CDKN1C/p57, RASSF1, and GPR62. Methylation of CpG islands associated with the genes is indicative of the grade or stage of the prostate cancer, and/or the length of disease-free survival following treatment for prostate cancer.

> Obtaining information about the aggressiveness of the cancer, its grade, and its stage is helpful when choosing a course of treatment. The patterns of CpG methylation may be correlated to the pathological stage and grade of the tumor. For example, in prostate cancer, patterns of CpG methylation may be correlated to the Gleason score of the primary tumor. The molecular information derived from CpG methylation may also be correlated to the likelihood of survival and the length

of disease-free survival following treatment. The above prognostic methods can enable the prediction of the course of the cancer, as well as the prediction of the best approach to treatment.

Also provided are methods of assessing the efficacy of 5 treatment of cancer by assaying for the reduced methylation of CpG islands that indicates efficacy of treatment. Generally, the method comprises providing a first and a second biological sample from a subject in need of assessing the efficacy of treatment of cancer and assaying the samples for a change in 10 methylation level of a CpG island associated with at least one gene selected from the group consisting of: NRG1, ADRB3, GFRA2, KIF13B, RET, GPR147, NEUROG3, PALD, HEMK1, FGF4, HTR1A, RNF180, DKFZP5640822, ZNF596, LOC441320, TDH, F1136980, FGF20, EFHA2, 15 ASAH1, NODAL, LOC399783, ISL2, KIFC2, C20orf23, GFRA1, GPX7, DKK2, NTN1, MMP9, TNFSF11, RHOD and LRRC49. Generally, the first biological sample is taken (e.g., prior to commencing treatment or during treatment) before the second biological sample, and the second biologi- 20 cal sample is taken after a course of treatment. In preferred embodiments, the method includes assaying for a change in methylation of CpG islands associated with two, three, four, five, six, seven, eight, nine, ten, eleven, or more of the foregoing genes. A decrease or absence of methylation of the 25 assayed one or more CpG islands in the second sample (i.e., following the course of treatment) indicates that the treatment is effective. Alternatively, the maintenance or increase of methylation in the assayed CpG islands in the second sample can indicate a reduction or absence of treatment efficacy.

The invention provides a method of assessing the efficacy of treatment of prostate cancer in a male mammal by assaying for the reduced methylation of CpG islands that indicate efficacy of treatment of prostate cancer. In one embodiment, the method comprises assaying biological samples, which are 35 taken from the male mammal periodically during the course of treatment, for methylation of a CpG island associated with at least one gene selected from the group consisting of: NRG1, ADRB3, GFRA2, KIF13B, RET, GPR147, NEU-ROG3, PALD, HEMK1, FGF4, HTR1A, RNF180, 40 DKFZP5640822, ZNF596, LOC441320, TDH, F1136980, FGF20, EFHA2, ASAH1, NODAL, LOC399783, and ISL2. In addition to or instead of the foregoing, the method can include assaying the biological samples for methylation of a CpG island associated with at least one gene selected from the 45 group consisting of: KIFC2, C20orf23, GFRA1, GPX7, DKK2, NTN1, RASSF5, HTRA4, MMP9, TNFSF11, RHOD and LRRC49. For example, the method of assessing the efficacy of treatment of prostate cancer includes assaying the biological sample for methylation of a CpG island asso- 50 ciated with NRG1, KIF13B, or both. In another example, the method includes assaying for a CpG island associated with at least one gene selected from the group consisting of: TDH, ASAH1, FGF20, HEMK1, PALD NEUROG, EFHA2, KIFC2, GFRA1, DKK2, TNFSF11, NTN1, and RHOD. In 55 preferred embodiments, the method can include assaying for methylation of CpG islands associated with two, three, four, five, six, seven, eight, nine, ten, eleven, or more of the foregoing genes. Generally, the assayed biological samples in the method include a first and a second biological sample. The 60 first biological sample can be taken, for example, prior to commencing treatment or during treatment, though in any event prior to taking the second biological sample. The second biological sample is taken during or after a course of treatment. A decrease or absence of methylation of the 65 assayed one or more CpG islands in the second sample (i.e., following the course of treatment) as compared to the first

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sample indicates that the treatment is effective. Alternatively, the maintenance or increase of methylation in the assayed CpG islands in the second sample as compared to the first sample can indicate a reduction in or absence of treatment efficacy.

The foregoing method of assessing the efficacy of prostate cancer treatment can optionally include, in combination with assaying for methylation of CpG islands associated with the foregoing genes, further assaying the biological sample for reduced methylation of a CpG island associated with at least one gene that is known to be (i) methylated in prostate cancer and (ii) not detectably methylated or methylated at a lower level (e.g., about 50% or less, about 40% or less, about 30% or less, about 20% or less, or less than about 10%) in BPH. In this regard, when the method includes assaying the biological samples for methylation of at least one CpG island that is known to be methylated in prostate cancer but known not to be detectably methylated or methylated at a lower level in BPH, the method preferably includes assaying for methylation of CpG islands associated with at least three different genes. Examples of CpG islands known not to be methylated in prostate cancer but not detectably methylated or methylated at a lower level in BPH include GSTP1, GPX3, GSTM1, GSTM4. CSMD1. TNFRSF10A. TNFRSF10B. TNFRSF10C, TNFRSF10D, SFRP1, SFRP2, DKK3, PTGS2, CDKN1C/p57, RASSF1, and GPR62. A decrease or absence of methylation of the CpG islands associated with the assayed genes in the second sample as compared to the first sample following some or all of the course of treatment indicates that the treatment is effective. Alternatively, the maintenance or increase of methylation in the assayed CpG islands in the second sample as compared to the first sample can indicate a reduction or absence of treatment efficacy.

CpG islands (Bird, Nature 321: 209-213 (1986); and Gardiner-Garden et al., J. Molec. Biol. 196: 261-282 (1987)) comprise about 1% of vertebrate genomes and account for about 15% of the total number of CpG dinucleotides. CpG islands typically are between about 0.2 and about 2.0 kb in length. They can be located upstream of (e.g., in a promoter or enhancer region) of the coding sequence of the associated genes or they may also extend into or be found within genecoding regions of their associated genes. A gene-coding region can include exons and introns. Use of the phrase "associated with" to describe a CpG island's relation to a gene, is intended to encompass CpG islands that are upstream of gene coding sequences as well as internal CpG islands. For example, the CpG island associated with the RET gene is internal and not expected to affect the expression of the RET gene when methylated. Some CpG islands are associated with the promoter of two genes and it can affect the expression of both genes. CpGs were labeled based on their location with respect to the nearest gene. In some cases, a CpG island may be located near the promoter of two different genes and may in this case influence the expression of both genes. In such case, the CpG island was named after one of the genes. For example, the LRRC49 CpG island is also associated with the THAP domain containing 10 (THAP10) gene. A CpG island can also be associated with a pseudogene or be located in a genomic region that includes no known genes or pseudogenes. The CpG island can still be of interest so long as its methylation status correlates with a disease status.

A CpG island can be separated by up to 25 kilobases (kb) (e.g., up to 20 kb, up to 19 kb, up to 18, kb, up to 17 kb, up to 16 kb, up to 15 kb, up to 10 kb, up to 9 kb, up to 8 kb, up to 7 kb, up to 6 kb, up to 5 kb, up to 4 kb, up to 3 kb, up to 2 kb, or up to 1 kb) from the transcription start site for the nearest gene and still be considered "associated with" the gene. Preferably,

CpG islands associated with at least three genes are assayed. However, CpG islands associated with 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or even more genes can be assayed.

Methods of identifying CpG islands have been described 5 (e.g., Takai et al., Proc. Nat'l. Assoc. Sci. USA, 99:3740-3745 (2002)). For example, genomic sequences can be analyzed to identify segments containing CpG islands that are at least 200 bp in length, have at least a 60% GC content, and contain at least 7% CpG dinucleotides. Preferred sequences are at least 10 250 bp in length, are at least 60% GC rich, and contain at least 7% CpG dinucleotides. Moreover, undesirable highly repetitive sequences can be screened out using a repeat masker that filters out sequences. Desirable sequences contain less than 50% repeats (i.e., a sequence of reduced complexity or a 15 sequence that is present at multiple genomic locations) within the length of the identified CpG island. Preferably, the CpG island is no more than 45%, 40%, 35%, 30%, 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, or 11% repetitive. Most desirable sequences are no more than 10% repeti- 20 tive. Examples of repetitive sequences are available, for example, at the web site for National Center for Biotechnology Information (NCBI).

"Biological sample" is intended to encompass any suitable sample that enables accurate assay of CpG island methylation. Examples of suitable biological samples include, but are not limited to, whole blood, blood plasma, blood serum, urine, saliva, cells (e.g., cells obtained from blood, such as epithelial cells), and tissue. Such samples are obtained in accordance with methods known in the art. When the biological sample is whole blood, blood plasma, or urine, preferably, CpG islands associated with more than three genes are assayed.

A CpG island is "not detectably methylated" when it is not methylated or it is methylated at a level below the level of 35 sensitivity of the assay method employed.

"Noncancerous" tissue can be benign or normal. Alternatively, but not preferably, the tissue can be diseased, as long as it is not cancerous.

Methods of assaying methylation of CpG islands are 40 known in the art and include, for example, restriction enzyme-based technology, such as one that employs digestion with a methylation-sensitive restriction endonuclease coupled with Southern blot analysis, methylation-sensitive enzymes and polymerase chain reaction (PCR), such as 45 methylation-sensitive arbitrarily primed PCR (AP-PCR; see, e.g., Gonzalgo et al., Cancer Res., 57: 594-599 (1997)), restriction landmark genomic scanning (RLGS; see, e.g., Plass et al., *Genomic* 58: 254-262 (1999)), methylated CpG island amplification (MCA; see, e.g., Toyota et al., Cancer 50 Res., 59: 2307-2312 (1999)), differential methylation hybridization (DMH; see, e.g., Huang et al., Human Mol. Genet., 8: 459-470 (1999)), and Not I-based differential methylation hybridization (see, e.g., International Patent Publication No. WO 02/086163). Other methods are described in U.S. Pat. 55 App. Pub. No. 2003/0170684 and International Patent Publication No. WO 04/05122.

Alternatively, cytosine conversion-based technology can be used. Such technology relies on methylation status-dependent chemical modification of CpG islands (i.e., deamination of unmethylated cytosines in CpG islands) within isolated genomic DNA or fragments thereof followed by DNA sequence analysis. Such methods employ reagents like hydrazine and bisulfite. Bisulfite treatment followed by alkaline hydrolysis is described by Olek et al., *Nucl. Acids Res.*, 24: 65 5064-5066 (1996); and Frommer et al., *PNAS USA*, 89: 1827-1831 (1992). The use of methylation-sensitive primers to

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assay methylation of CpG islands in isolated genomic DNA is described by Herman et al., *PNAS USA*, 93: 9821-9826 (1996), and in U.S. Pat. Nos. 5,786,146 and 6,265,171. Bisulfite-treated DNA can be subsequently analyzed by conventional molecular techniques, such as PCR amplification, fluorescence-based, real-time PCR (see, e.g., Eads et al., *Cancer Res.*, 59: 2302-2306 (1999); Heid et al., *Genome Res.*, 6: 986-994 (1996); and U.S. Pat. No. 6,331,393), sequencing, oligonucleotide hybridization detection, and methylation-sensitive single nucleotide primer extension (Ms-SNuPE; see, e.g., Gonzalgo et al., *Nucl. Acids Res.*, 25: 2529-2531 (1997); and U.S. Pat. No. 6,251,594).

A preferred method of assaying for methylation of a CpG island includes isolating genomic DNA (and/or fragments thereof) from a biological sample, treating the DNA under deaminating conditions that convert unmethylated cytosines to uracil, using the treated DNA as a template in a PCR reaction to amplify a target sequence that includes the CpGisland of interest, thereby producing an amplified sequence. Unmethylated cytosines in the target sequence, which are converted to uracils by the deaminating treatment, are amplified as thymines in the corresponding position of the amplified sequence. Since the sequence of the forward and the reverse strand of the CpG island lose their complimentarity after the deamination reaction, the methylation status of the CpG island can be determined by assaying one or both of the original strands by utilizing primers capable of annealing to the strand of interest.

The deamination reaction may not proceed to completion, which results in false positives. For example, deamination of DNA sequences using bisulfite salt is sensitive to the purity of the DNA, length of incubation, and the secondary structure of the denatured templates. Quantitative PCR methods can be used to assay for the efficiency of deamination. However, quantitative PCR methods are limited to assaying the conversion status within the sites where the primers and probes anneal to the template.

Quantitative PCR methods are also limited to assaying for the methylation of cytosines within the sites where the primers and probes anneal to the template. The primers and the probe only anneal efficiently to the templates that are fully converted and contain methylation at the appropriate cytosine nucleotides. Thus, they fail to provide methylation information for CpG dinucleotides that are not assayed for. The CpG islands may also be analyzed using direct sequencing following the deamination treatment. However, due to the heterogeneity of the methylation pattern within a CpG island and the presence of homopolymeric stretches within the sequence, direct sequencing of CpG islands can yield a sequencing pattern that is too noisy and complex for the available sequencing software.

To overcome these disadvantages and to minimize the overall cost of analysis for a clinical test, we developed a method to analyze the amplified sequences by terminationcoupled linear amplification. The DNA is linearly amplified using a forward or a reverse primer in the presence of dNTPs and one or two dideoxynucleotides such as dideoxycytidine or dideoxyguanine. The amplified sequence can, optionally, be analyzed using only thymine and/or cytosine terminators when assaying for a methylated CpG dinucleotide (or adenine and/or guanine terminators when analyzing the amplified strand opposite to the CpG dinucleotide of interest) to make extension reaction products that terminate at thymines and/or cytosines nucleotides (or at guanine and/or adenine when assaying the opposite strand). The amplification reaction results in the generation of fragments with multiple lengths, each length of which corresponds to the distance in bases

between the primer used for amplification and the position within the target sequence of a nucleotide that is complementary to the dideoxynucleotide added to the amplification reaction. Such amplification can result in the generation of 10 to 20 fragments from an average CpG island-containing ampli- 5 con of 100 to 150 bp. The extension products can be separated by size on an acrylamide gel and compared to (a) a size standard and/or (b) by comparing the fragments to those generated when fully unmethylated (PCR generated template or clones in E. coli) or fully methylated (enzymatically methylated in vitro) template to thereby determine the presence of cytosine (or guanine on the opposite strand) or the presence of thymine (or adenine on the opposite strand) in the amplified CpG island-containing sequence. When bisulfite is used as the deaminating agent, the amplified sequence may 15 contain large stretches of thymine or adenine which may result in additional fragments due to the DNA polymerase slippage during amplification. Such "stutter" patterns may be minimized by selectively analyzing segments of the CpG islands that have shorter homopolymeric sequences. Stutter 20 fragments can also be identified by analyzing the control templates.

When a fluoresent label is used to tag the primers or the dideoxynucleotides used in the terminator-coupled linear amplification, the resulting fragments may be analyzed using 25 automated sequencing machines and software designed for determining the size of DNA fragments. In this regard, commercially available software such as GENESCAN (Applied Biosystems, Foster City, Calif.) and GENEMAPPER (Applied Biosystems) are trained to recognize and account for 30 stutter patterns due to DNA polymerase slippage during the amplification of microsatellite repeats. Such software may also be used to account for the stutter pattern that is observed when amplifying homopolymeric stretches of DNA, as might be seen after bisulfite conversion of CpG islands. There are a 35 number of fluorescent dyes available for the automated analysis of DNA such as but not limited to 6-carboxyfluorescein (6-FAM), Hexachlorofluorescein (HEX), VIC dye, 5-carboxytetramethylrhodamine (TAMRA), 5-carboxy-Xrhodamine, succinimidyl ester (5-ROX), 6-carboxy-2',4,7,7'- 40 tetrachlorofluorescein (TET). The methods and equipment to determine amplicon size have been available for over a decade and in use for genetic linkage mapping, DNA identity, and forensic. For example, Applied Biosystems has a set of 5 dyes that can be used to multiplex fragments from 4 separate 45 amplification reaction and one standard for use in linkage mapping on the ABI sequencers. Four different CpG islands from a single individual can be linearly amplified using fluorescently tagged primers, and the products pooled before analysis. Alternatively, different CpG islands from different 50 individuals can be linearly amplified using fluorescently tagged primers, and the products pooled before analysis.

Since methylation of a particular CpG dinucleotide is not always complete in a sample, i.e., the CpG sequence is heterogenous, the methods provided herein can be advantageously used to analyze the extent of or percent methylation of a particular CpG dinucleotide site within a sample. In a preferred method, two different fluorescent-dye terminators are used for thymine and cytosine, respectively (or adenine and guanine, respectively, when analyzing the opposite 60 strand) in a fluorescent dideoxy sequencing reaction. The relative abundance of the two dyes in same-size extension products are indicative of the relative abundance of the two nucleotides at a particular sequence position, and can thereby indicate the percent methylation of a particular CpG dinucleotide site within a CpG island. To determine the expected relative abundance of the two dyes, control reactions with a

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range of known ratios of fully methylated to fully unmethlylated templates can be used. The data obtained from the control reactions can be used as a reference to estimate relative abundance of methylated and unmethylated cytosines in a sample.

The levels of methylation or patterns of methylation at given CpG islands can be assayed as appropriate. The assay can employ the use of a reference standard when appropriate to enable the determination of abnormal methylation. A reference standard can be determined based on reference samples obtained from age-matched noncancerous classes of adjacent tissues, and with normal peripheral blood lymphocytes. When, for example, efficacy of treatment is being assessed, the assay results of biological samples taken over the course of treatment can be compared without the use of a reference standard.

When the DNA obtained from a biological sample is in limited quantities and is not sufficient for the analysis of multiple markers, the methods described herein can include amplifying the DNA from the sample. Amplification can be done using PCR amplification or isothermal amplification methods, for example, those described in U.S. Pat. Nos. 5,854,033; 6,124,120; 6,143,495; 6,210,884; 6,642,034; 6,280,949; 6,632,609; and 6,642,034; and U.S. Pat. App. Pub. Nos. 2003/0032024; 2003/0143536; 2003/0235849; 2004/ 0063144; and 2004/0265897, which are incorporated herein by reference in their entirety. Isothermal amplification can include rolling circle or strand displacement amplification. Methods that combine PCR and isothermal amplification have also been described (U.S. Pat. Nos. 6,777,187; and 6,828,098; and U.S. Pat. App. Pub. Nos. 2004/0209298; 2005/0032104; and 2006/0068394, each of which is incorporated herein by reference in its entirety). U.S. Pat. App. Pub. No. 2005/0202490, which is incorporated herein by reference in its entirety, describes the use of such methods in combination with methylation-sensitive restriction enzymes to study the methylation pattern of DNA. DNA amplification can also include methylation-coupled whole genomic amplification to generate the DNA needed, such as described in U.S. Pat. App. Pub. No. 2006/0257905, which is incorporated by reference herein in its entirety. The methylation-coupled whole genomic amplification can be especially advantageous when DNA is recovered from minute biological samples or from bodily fluids such as urine or plasma.

Skilled artisans will appreciate that the various amplification methods described herein, e.g., the PCR amplification, isothermal amplification, and termination-coupled linear amplification method, can employ nucleotides, nucleotide analogues, nucleotide or nucleotide analogue derivatives, and/or combinations thereof.

If desired, mRNA and protein levels can be assayed, and alterations in their expression levels can be indicative of a change in the level of methylation or the patterns of methylation at given CpG islands. Such methods of assaying mRNA and protein levels are also within the skill in the art. For example, the mRNA assay methods described in U.S. Provisional Patent Application No. 60/705,964 filed on Aug. 5, 2005 and International Patent Publication No. WO 2007/019444, which are hereby incorporated by reference, can be used. Such methods are particularly useful if a degraded tissue sample is used as the biological sample. Alternatively, reverse transcription with gene-specific primers can be used to assay mRNA levels. Proteins levels can be assayed, for example, using antibody and staining techniques.

It is important to note that even though aberrant methylation of a CpG island can affect expression of the associated gene, the methods described herein are not dependent on a

biological role for the hypermethylation. That is a hypermethylated CpG island can be useful in the methods of the invention regardless of its effect on gene expression. Accordingly, the only requirement is that there be a correlation between the methylated state of a CpG island and the presence of cancer.

The invention further provides target sequences and corresponding primers or probes that are useful in the above methods. The target sequences provide the context for the selection of CpG islands to assay for methylation. If a given target 10 sequence contains more than one CpG island, all or less than all of the CpG islands, even one CpG dinucleotide, can be assayed for methylation with respect to that particular target sequence. In this regard, a target sequence can include a genomic sequence that is fully methylated and fully deaminated such as SEQ ID NO: 1 or 2 [NRG1], SEQ ID NO: 3 or 4 [ADRB3], SEQ ID NO: 5 or 6 [GFRA2], SEQ ID NO: 7 or 8 [KIF13B], SEQ ID NO: 9 or 10 [RET], SEQ ID NO: 11 or 12 [GPR147], SEQ ID NO: 13 or 14 [NEUROG3], SEQ ID NO: 15 or 16 [PALD], SEQ ID NO: 17 or 18 [HEMK1], SEQ 20 ID NO: 19 or 20 [FGF4], SEQ ID NO: 23 or 24 [HTR1A], SEQ ID NO: 25 or 26 [RNF180], SEQ ID NO: 27 or 28 [ECOP], SEQ ID NO: 29 or 30 [ZNF596], ID NO: 33 or 34 [LOC441320], SEQ ID NO: 35 or 36 [TDH], SEQ ID NO: 37 or 38 [FLJ36980], SEQ ID NO: 39 or 40 [FGF20], SEQ ID 25 NO: 41 or 42 [EFHA2], SEQ ID NO: 43 or 44 [ASAH1], SEQ ID NO: 45 or 46 SEQ ID NO: 49 or 50 [NODAL], SEQ ID NO: 51 or 52 [LOC399783], SEQ ID NO: 53 or 54 [ISL2]. These fully methylated and deaminated sequences are used for illustrative purposed and do not exclude the use of par- 30 tially methylated and deaminated sequences in the methods of the invention. A target sequence can include a genomic sequence that is partially methylated, such as in DNA obtained from a tumor, and then deaminated such that the target differs from the sequence listed above. Persons of skill 35 in the art will appreciate that a target sequence that includes a partially methylated and deaminated CpG island will result in a population of DNA molecules that differ at one or more positions that correspond to the cytosine residues in one or more CpG dinucleotides. Thus, a target sequence can include 40 a variety of partially methylated and deaminated sequences based on the following genomic sequences SEQ ID NOs: 119 or 220 [KIFC2], SEQ ID NOs: 121 or 122 [C200RF23], SEQ ID NOs: 123 or 124 [GFRA1], SEQ ID NOs: 129 or 130 [DKK2], SEQ ID NOs: 133 or 134 [RASSF5], SEQ ID NOs: 45 135 or 136 [NTN1], SEQ ID NOs: 139 or 140 [GPR147], SEQ ID NOs: 141 or 142 [NEUROG3], SEQ ID NOs: 143 or 144 [NODAL], SEQ ID NOs: 145 or 146 [PALD], SEQ ID NOs: 147 or 148 [LOC399783], SEQ ID NOs: 151 or 152 [LOC441320], SEQ ID NOs: 153 or 154 [ZNF596], SEQ ID 50 NOs: 155 or 156 [TDH], SEQ ID NOs: 157 or 158 [ASAH1], SEQ ID NOs: 159 or 160 [FGF20], SEQ ID NOs: 161 or 162 [FLJ36980], SEQ ID NOs: 163 or 164 [GFRA2], SEQ ID NOs: 165 or 166 [EFHA2], SEQ ID NOs: 171 or 172 [KIF13B], SEQ ID NOs: 173 or 174 [ADRB3], SEQ ID NOs: 55 175 or 176 [NRG1], SEQ ID NOs: 177 or 178 [ECOP], SEQ ID NOs: 179 or 180 [HTR1A], SEQ ID NOs: 181 or 182 [ISL2], SEQ ID NOs: 183 or 184 [LOC285671], SEQ ID NOs: 185 or 186 [FGF4], SEQ ID NOs: 189 or 190, [HEMK1], SEQ ID NOs: 191 or 192 [RET] SEQ ID NOs: 60 193 or 194 [HTRA4], SEQ ID NO: 195 [RHOD], SEQ ID NO: 196 TNFSF11, SEQ ID NO: 197 [MMP9], and SEQ ID NO: 198 [LRRC49].

These targets can be used in combination with known targets (for example known CpG islands associated with 65 GSTP1, GPX3, GSTM1, GSTM4, CSMD1, TNFRSF10A, TNFRSF10B, TNFRSF10C, TNFRSF10D, SFRP1, SFRP2,

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DKK3, PTGS2, CDKN1C/p57, RASSF1, and GPR62. For example, fully methylated and deaminated sequences for some of these genes are provided in SEQ ID NO: 31 or 32 [CSMD1], SEQ ID NO: 45 or 46 [TNFRSF10C], SEQ ID NO: 47 or 48 [TNFRSF10B] SEQ ID NO: 21 and 22 [GPR62]. Also for example, a target sequence can include fully or partially methylated and (subsequently) deaminated sequences based on the following genomic sequences SEQ ID NOs: 131 or 132 [GPX3], SEQ ID NOs: 125 or 126 [GPX7], SEQ ID NOs: 127 or 128 [GSTM4], SEQ ID NOs: 137 or 138 [SFRP2], SEQ ID NOs: 149 or 150 [CSMD1], SEQ ID NOs: 167 or 168 [TNFRSF10B], SEQ ID NOs: 169 or 170 [TNFRSF10C], and SEQ ID NOs: 187 or 188 [GPR62]. Such target sequences can be isolated or purified in accordance with methods known in the art.

Also provided are isolated or purified primers derived from and suitable for amplifying sequences internal to the above isolated or purified nucleic acid molecules. The isolated or purified primers can be DNA, RNA, PNA, and the like. It will be understood by one of ordinary skill in the art, however, that one type of nucleic acid can be preferred over another, depending on the particular biological sample, the methodology employed in assaying CpG islands for methylation, and the ability of the particular type of nucleic acid to detect methylation. One or more (e.g., two, three four, four, five, six, seven, eight, nine ten or more) isolated pairs of primers can be provided. Optionally, primers are provided as part of a kit useful in the methods disclosed herein. The pair of primers can consist essentially of SEQ ID NOs: 55 and 56, SEQ ID NOs: 57 and 58, SEQ ID NOs: 59 and 60, SEQ ID NOs: 61 AND 62, SEQ ID NOs: 63 and 64, SEQ ID NOs: 65 and 66, SEQ ID NOs: 67 and 68, SEQ ID NOs: 69 and 70, SEQ ID NOs: 71 and 72, SEQ ID NOs: 73 and 74, SEQ ID NOs: 75 and 76, SEQ ID NOs: 77 and 78, SEQ ID NOs: 79 and 80, SEQ ID NOs: 81 and 82, SEQ ID NOs: 83 and 84, SEQ ID NOs: 85 and 86, SEQ ID NOs: 87 and 88, SEQ ID NOs: 89 and 90, SEQ ID NOs: 91 and 92, SEQ ID NOs: 93 and 94, SEQ ID NOs: 95 and 96, SEQ ID NOs: 97 and 98, SEQ ID NOs: 99 and 100, SEQ ID NOs: 101 and 102, SEQ ID NOs: 103 and 104, SEQ ID NOs: 105 and 106, or SEQ ID NOs: 107 and 108. It is understood that these primer pairs are examples of suitable primers for use in the context of the invention. For example, each primer can be between 10 and 40 nucleotides and together the pair of primers can flank a region of at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 130, 140, 150, 200, 250, 300 by in length that includes one or more CpG dinucloetides in a CpG island of interest. Primer pairs can be modified in various ways, such as by chemical modification of a base, and still be useful in the context of the invention. Other primers derived from the target sequences, namely SEQ ID NOs: 1-54 and 119-198, and variants thereof, also can be used in the context of the invention. The only requirement is that such primers function to assay for methylation of a given CpG island. Thus, for example, alternate primers can be selected or the provided primers can be modified or provided in degenerate form to account for target sequence polymorphisms within a given population, so long as the primers are still suitable for assaying modification of CpG islands associated with the genes disclosed herein.

Like the target sequences, the primer pairs can be isolated or purified in accordance with methods known in the art. Alternatively, they can be synthesized using routine methods.

The primers can be part of a kit. Preferably, the kit comprises at least three pairs of primers, wherein each primer pair is specific for a CpG island associated with a different gene. However, the kit can comprise additional primer pairs, such as primer pairs for other CpG islands associated with the same

gene or primer pairs for amplifying CpG islands associated with four, five, six, seven, eight, nine, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or even more genes. The kit can further comprise one or more reagents for assaying for methylation of CpG islands, instructions for use, 5 and/or other components as are typically found in kits. For example, the kit can comprise a buffer suitable for (a) isolating genomic DNA comprising a target sequence from a biological sample, (b) amplifying a portion of the target sequence, and/or (c) deaminating a target sequence. In 10 embodiments directed to the evaluation of prostate cancer, a kit can comprise one or more buffers suitable for preparing genomic DNA from serum and/or urine samples.

EXAMPLES

The following examples serve to illustrate the invention.

The examples are not intended to limit the scope of the invention.

Example 1

This example demonstrates the determination of the methylation status of markers based on methylation-specific PCR amplification. Paraffin-embedded prostate tissues were 25 obtained following radical prostatectomies. The tissue samples were sectioned into 23 10-micron sections and slide 1, 12, and 23 were stained using hematoxylin and eosin (H&E). Using the H&E slides as guide, the areas corresponding to the tumor tissues were microdissected from the 30 unstained slides. The remaining tissues were recovered to use as a normal paired sample. Following deparaffinization using two xylene extractions and two ethanol washes, the DNA was isolated from the tumor tissue and surrounding normal tissues using standard proteinase K digest for 5 days at 50° C.,

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extraction with phenol/chloroform and ethanol precipitation (*Current Protocols in Molecular Biology*, edited by Ausubel, et al., Wiley-Interscience (New York 1988, revised 1988-2006)). The DNA was resuspended in TE8 and the quality and quantity of the DNA was assessed by agarose gel electrophoresis using concentration and size standards as reference. Following denaturation in the presence of 0.3 M NaOH, the DNA was treated with 2.5 M sodium metabisulfite, pH 5.5, in the presence of 1 mM hydroquinone at a concentration of 1 µg of DNA/500 µl. The reaction was incubated in a thermocycler for a total of 8 cycles (95° C. for 5 minutes; 55° C. for 115 minutes).

Following bisulfite treatment, the DNA was purified using the QIAEX II purification kit (Qiagen, Valencia, Calif.) according to the manufacturer's recommendations and eluted in 50 µl of TE8. Sodium hydroxide (5.5 µl of 2 N) was added, and the DNA was incubated at RT for 15 min. The DNA was then precipitated with 3 volumes of ethanol and 0.3 volumes of 5 M NH₄OAC. The DNA was resuspended in 50 µl of TE8 and stored at -20° C.

In order to determine if a specific CpG position is methylated in genomic DNA isolated from tumor tissue, methylation-specific polymerase chain reaction (PCR) was performed, using primers designed to overlap the position of the CpG island of interest. All PCR reactions were performed in a MASTERCYCLER thermocycler (Eppendorf, Westbury, N.Y.) for 42 cycles of 95° C. for 15 seconds, 63° C. for 30 seconds, and 72° C. for 10 seconds. Each reaction was carried out in 30 µl of 1× PLATINUM Taq PCR buffer containing 1.5 mM magnesium chloride, 0.25 mM dNTPS, 12.5 pmoles of each primer, and 0.5 units of PLATINUM Taq enzyme (Invitrogen, Carlsbad Calif.). The primers used for each CpG island and the size of the product are shown in Table 1, wherein "F" indicates forward primer, "R" indicates reverse primer, "m" indicates methylated, and "u" indicates unmethylated.

TABLE 1

Gene associat	ed ndPrimer sequences	Annealing temperature (° C.)	Product size (bp)
NRG1	mF: GAGCGGGTAGCGAGAGTTTCGG [SEQ ID NO: 55] mR: TAACGACGCGACTACCGAAAACC [SEQ ID NO: 56]	63	119
ADRB3	mF: GATTAACGTGTTCGTGATTTCGTT [SEQ ID NO: 57] mR: CAACGACCAATAACCAATCAACGCC [SEQ ID NO: 58]	63	102
GFRA2	mF: ATACGTCGGTGAGTTCGGTTTATC [SEQ ID NO: 59] mR: ACTCCCGACTCCCTAAACTCCGAA [SEQ ID NO: 60]	63	101
KIF13b	mF: TGAATCGGCGAGGTGAGAGTCG [SEQ ID NO: 61] mR: ACCGAACGTCTCAACGCGAAAACG [SEQ ID NO: 62]	65	179
RET	mF: TATCGTTAGCGTCGTGGTGGAGTT [SEQ ID NO: 63] mR: CTACACGAACACTAAACCGACCGA [SEQ ID NO: 64]	63	120
GPR147	mF: TCGGTCGTTACGTTGATCGTTATTC [SEQ ID NO: 65] mR: ACCCTACGCATACCCTTCTCGAAC [SEQ ID NO: 66]	63	119
NEUROG3	mF: GTTTCGAGGAAGTTTCGGGTACGG [SEQ ID NO: 67]	63	103

TABLE 1-continued

Gene associa		Annealing temperature	
with CpG isi	andPrimer sequences	(* 6.)	size (bp)
	mR: GATCGTTAACCTTCTTTCGCCGAC [SEQ ID NO: 68]		
PALD	mF: CGAAGTTGGGAGGAGCGAGTT	63	115
	[SEQ ID NO: 69] mR: AAACATCCGTACTCCTACGACCGA		
	[SEQ ID NO: 70]		
HEMK	[tif: CGTATTAGTCGTATTCGCGAGCGT	63	99
	[SEQ ID NO: 71] mR: CGAAACTACTCGACCCGACCC		
	[SEQ ID NO: 72]		
FGF4	mF: TAACGGTACGTTGGAGGTCGAGTT	63	102
	[SEQ ID NO: 73] mR: ACGACCGCCTCCTTAAACTACGCT		
	[SEQ ID NO: 74]		
GPR62	mF: TATCGTGTATTCGTTGCGGTTAGG	63	120
	[SEQ ID NO: 75]		
	mR: AACGATACGAACGACGTACCGAA [SEQ ID NO: 76]		
HTR1A	mF: TACGTGAATAAGAGGACGTTTCGG	63	115
	[SEQ ID NO: 77]		
	mR: AACGATCTTCCGAAATACGCCAA [SEQ ID NO: 78]		
RNF180	mF: TCGTCGAATCGGTATCGTCGTC	63	118
	[SEQ ID NO: 79] mR: ACCTATATCCACGTCCCGAAACCT		
	[SEQ ID NO: 80]		
ECOP	mF: CGGTTGTAGTTTGTTCGTTCGTTTC	63	108
	[SEQ ID NO: 81] mR: CTAACGCCTCATAACTCCTCGCGT		
	[SEQ ID NO: 82]		
ZNF596	mF: GCGTCGATTCGGGAGTAGTATCGT	63	96
	[SEQ ID NO: 83] mR: ATACCGTAAATCCGCGCTACTTCC		
	[SEQ ID NO: 84]		
CSMD1	mF: CGTTGAGGTCGAATGAAGCGTAGT	63	96
	[SEQ ID NO: 85] mR: AACCGAAACTAAACACGACGCAA		
	[SEQ ID NO: 86]		
LOC441320	mF: AAGCGTATAGTTCGAGGATTGCGA	63	107
	[SEQ ID NO: 87] mR: CCGCGTCACTTACTCCTCTACGA		
	[SEQ ID NO: 88]		
TDH	mF: CGTTGGGTGCGTAGGAAGGTTAGT	63	120
	[SEQ ID NO: 89] mR: GACCGACCCTAAACAACCCGCT		
	[SEQ ID NO: 90]		
FLJ36980	mF: GTTGCGGGATAGCGTTGTGATT	63	96
	[SEQ ID NO: 91] mR: ACCATTATCAATACTCCGATCGCC		
	[SEQ ID NO: 92]		
FGF20	mF: TTTGTTTGTTAAGGGCGTTATCGT	63	105
	[SEQ ID NO: 93] mR: CCGCGACTACTCTAACCAACCC		
	[SEQ ID NO: 94]		
EFHA2	mF: GGGCGTTGAGTTTAGTTCGGAGA	63	108
	[SEQ ID NO: 95] mR: ACGAACACAACCGAATCAACGTAA		
	[SEQ ID NO: 96]		

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TABLE 1-continued

Gene associa	ited	Annealing temperature	Product				
	andPrimer sequences		size (bp)				
ASHA1	mF: GGCGTTGGTTGTTAGAGCGATG [SEQ ID NO: 97] mR: GACTCAAACTCACTCACCGACGAC [SEQ ID NO: 98]						
TNFRSF10C	mF: GGTGCGATTTAGGATTTAGGACGG [SEQ ID NO: 99] mR: GCGACCGAAACTCACTAACAACAA [SEQ ID NO: 100]	63	115				
TNFRSF10B	mF: GCGATTTGGGTCGTTAGGGAATAG [SEQ ID NO: 101] mR: ACCTCTCCGTAACTTCACGCAACTT [SEQ ID NO: 102]	63	119				
NODAL	mF: GGTAGTCGCGGTCGTTTACGTT [SEQ ID NO: 103] mR: ACGAACAAACGACAAATCGAATCA [SEQ ID NO: 104]	63	111				
LOC399783	mF: TACGTTGAGTTCGGTTTGGTTTGT [SEQ ID NO: 105] mR: CGCGCCTCCGTAATCTAAACTAA [SEQ ID NO: 106]	63	103				
ISL2	mF: GTGCGTGTTGACGTTATGTTGCGT [SEQ ID NO: 107] mR: CGCCCGACCTCGACTCTTTACT [SEQ ID NO: 108]	63	99				
GSTP1	mF: CGGCGATTTCGGGGATTTTAGGGC [SEQ ID NO: 109] mR: GACCGCTCTTCTAAAAAATCCCGCG [SEQ ID NO: 110]	63	109				
GSTP1	mF: ACGTTCGGGGTGTAGCGGTCGTC [SEQ ID NO: 111] mR: CCCCAATACTAAATCACGACGCCG [SEQ ID NO: 112]	63	93				
GSTP1	mF: GGTCGGCGTCGTGATTTAGTATTGG [SEQ ID NO: 113] mR: ACTACGACGACGAAACTCCAACGA [SEQ ID NO: 114]	63	99				
GSTP1	uF: TGTGGTGATTTTGGGGATTTTAGGGT [SEQ ID NO: 115] uR: CCAACCACTCTTCTAAAAAATCCCACA [SEQ ID NO: 116]	63	113				
GSTP1	uF: GATGTTTGGGGTGTAGTGGTTGTTG [SEQ ID NO: 117] uR: CTCCACCCCAATACTAAATCACAACA [SEQ ID NO: 118]	63	99				
KIFC2	mF: TGATGGTCGTATTGCGGGTTTATC [SEQ ID NO: 199] mR: ATACCTAAACCCAACGCCGACTAC [SEQ ID NO: 200]	62	91				
C20orf23	mF: CGCGATTTGAGTAGTTAGCGTCGT [SEQ ID NO: 201] mR: AACCAACGCGACGACCTAACTAAC [SEQ ID NO: 202]	62	90				
GFRA1	mF: TAGATTTCGGTGTTTTCGGGCGTT [SEQ ID NO: 203] mR: CCGCTAATTCCCAATCGTACTACTCA [SEQ ID NO: 204]	62	98				
GPX7	mF: TTCGTTTCGTTCGGTCGTGATT [SEQ ID NO: 205] mR: GACTACGAACGCTTCGAATTCCTC [SEQ ID NO: 206]	62	116				

TABLE 1-continued

Gene associate	d dPrimer sequences	Annealing temperature (° C.)	Product size (bp)
DKK2	mF: GTTGCGTTGGTAGCGATTCGTTGT [SEQ ID NO: 207] mR: CCCGAACCGAATCCTCGAAATCT [SEQ ID NO: 208]	62	117
NTN1	mF: GACGTAGTATGATGCGCGTAGTGTG [SEQ ID NO: 209] mR: GCGAACATACTAAACCCGAACCC [SEQ ID NO: 210]	62	103
HTRA4	mF: GGATTACGTCGGTGTTCGATTTGT [SEQ ID NO: 211] mR: AACGCACGATTAACCCTACGCC [SEQ ID NO: 212]	62	95
ММР9	mF: TCGGATTAAGGTAGGCGTGGTTTC [SEQ ID NO: 213] mR: AACGTAAACGCCGAACCGAAC [SEQ ID NO: 214]	62	102
RHOD	mF: GGAAGACGTCGTTGTTGATGGTTT [SEQ ID NO: 215] mR: ACCGCTCCGACACGAACCTATAC [SEQ ID NO: 216]	62	120
TNSF11	mF: AGCGTTATGCGTCGCGTTAGTAG [SEQ ID NO: 217] mR: GCAAACGACGACGAAACGTACA [SEQ ID NO: 218]	62	116
SFRP2	mF: GAAGAGAGCGGGTTCGGGATAAG [SEQ ID NO: 219] mR: CTACAACATCGTAAACGCGCGAC [SEQ ID NO: 220]	62	101

The products of the PCR reactions were separated on 8% acrylamide gel. Only templates that exhibited methylation at all of the CpG islands that were present within the primers could serve as efficient templates for the amplification reactions. Control reactions were performed using fully methylated templates that were methylated in vitro using SS1 (CpG) methylase (NEB, Beverly, Mass.) according to the manufacturer's protocol. All primer pairs listed in Table 1 yielded a product of the correct size from fully methylated control template. Two negative controls (water and DNA 45 isolated from white blood cells) were included for each target PCR amplification, which did not yield a PCR product. When a CpG island is methylated in a DNA sample, an amplification product of the expected size is obtained. This example demonstrates that the above primers can be used to assay for 50 methylation of CpG islands in prostate cancer and that the CpG islands exhibit methylation in prostate cancer.

Example 2

This example demonstrates the determination of the methylation status of CpG islands at the ADRB3 locus by DNA sequencing. DNA is obtained from tumor samples and treated with sodium bisulfite as described in example 1. Two microliters of the bisulfite treated DNA are amplified with the 60 following primers: ADRB3-F1: GAGAAGAGGAAGGTA-GAAGGAG [SEQ ID NO: 221] and ADRB3-R1: CTAC-CTAACTATAACCAACCC [SEQ ID NO: 222] for 40 cycles as described in example 1 except for the annealing temperature, which is lowered to 55° C. The amplified 250 bp product 65 is purified using QIAquick PCR purification kit (Qiagen, Valencia Calif.) and recovered in TE8. Fifty nanograms of the

ADRB3 amplified product is sequenced using 1.25 pmole of ADRB3-F2:ACGGAGGAGGAGGATAGTACG [SEQ ID NO: 223] using BigDye Terminator v3.1 cycle sequencing kit (Applied Biosystems) and the sequencing reaction is purified using Centri-Sep columns (Applied Biosystems) according to the manufacturer's protocols. The products of the sequencing reaction are analyzed using an ABI 3700 sequencer according to manufacturer's specification. The resulting DNA sequence shows one or more sequence peaks corresponding to cytosine base or a mixed cytosine/thymidine base at the cytosine residue position of CpG dinucleotides that are fully or partially methylated in the original tumor DNA.

Alternatively, a more detailed sequence analysis is obtained by cloning the product of the amplification reaction using a TOPO TA cloning kit (Invitrogen, Carlsbad Calif.) according to supplier's protocol. Approximately 20 colonies are chosen for further analysis. Each colony is grown in 3 ml of LB media for 16 hours. DNA is isolated from 1.5 ml aliquot using plasmid preparation kit from Qiagen. The plasmid DNA is quantitated using spectrophotometer and 1 microgram aliquot is sequenced as described above. The sequence of the 20 individual clones is compared to determine which cytosines are methylated and to provide an estimate of their rate of methylation in the tumor sample. This example shows that the methylation status of cytosines within CpG islands can be determined using a sequencing approach.

Example 3

This example demonstrates the determination of the methylation pattern of multiple CpG islands associated with KIFC2, GFRA1 and GPX7 using terminator-coupled linear

amplification. From DNA from tumor samples prepared as described in example 1, fragments of the CpG islands associated with KIFC2, GFRA1, GPX7 are amplified individually using the mF1 and mR1 primers shown below for each CpG island. The amplification reactions are performed for 42 cycles as described in example 1 except for the annealing temperature, which was lowered to 58° C. An aliquot of the amplification reaction is separated on an 8% acrylamide gel to verify that fragments of the appropriate length are obtained (264 bp for KIFC2, 326 bp for GFRA1, 367 bp for GPX7).

The product of the PCR reaction were purified using QIAQUICK PCR purification kit (Qiagen).

Each amplification product (25 nanograms) is subjected to linear terminator-coupled amplification using 1.5 pmoles of the fluorescently labeled F2 primer shown below for the corresponding amplicon. The amplification reaction includes $1\times$ VentR (exo-) DNA polymerase (New England Biolabs, Beverly Mass.), 30 μM dATP, 37 μM dCTP, 100 μM dGTP, 100 μM dTTP, 480 μM ddCTP and 2 units of VentR (exo-) DNA polymerase. Reactions are performed in an MASTERCY-CLER thermocycler (Eppendorf) for 30 cycles of 95° C. for 15 seconds, 58° C. for 30 seconds, and 72° C. for 30 seconds. Following amplification, the reaction products are pooled into a single tube and purified using Centri-Sep columns (Applied Biosystems) according to the manufacturer's protocols. One microliter of GENESCAN 500 LIZ standard (Applied Biosystems) is added to one tenth of the purified fragment and the DNA separated using the ABI Prism 3100 Genetic Analyzer (Applied Biosystems) according to manufacture's instructions. The data is analyzed using the GENES-CAN and the GENEMAPPER software (Applied Biosys-

The following primers are used for the amplifications:

KIFC2-F1: AGGTA(C/T)GTTGTATTTGGTGGATTTGG	[SEQ	ID	NO:	224]	
KIFC2-R1: CCCACCTACAACAACAACACC	[SEQ	ID	NO:	225]	
KIFC2-F2: 6FAM-GAACGCGTACGGAAGGTAGG	[SEQ	ID	NO:	226]	
GFRA1-F1: GTGATAGGTTTGTAGATTTGATAGTTG	[SEQ	ID	NO:	227]	
GFRA1-R1: AACTAACCTCCATTTTAACTATTTC	[SEQ	ID	NO:	228]	
GFRA1-F2: NED-GAGAGATGAATTTGGATATTAGT	[SEQ	ID	NO:	229]	
GPX7-F1: GGTAAATTGGTGT(C/T)GTTGGAGAAG	[SEQ	ID	NO:	230]	
GPX7-R1: ACTAAACAATAATACCC (A/G) ACCTC	[SEQ	ID	NO:	231]	
GPX7-F2: VIC-GTCGTTGGGTTCGGTTTCGTTTTG	[SEQ	ID	NO:	232]	

The F1 and R1 primers are used for the amplification of a fragment of a CpG island from the tumor DNA. The F2 primers are used for termination-coupled linear amplification.

This example shows that termination-coupled linear amplification fragment lengths can be analyzed to (i) determine the presence and/or the positions of methylated cytosines in CpG islands in a sequence of interest as well as 65 (ii) provide information about the efficiency of the deamination reaction, since incomplete deamination results in frag-

ments with length that differ than what is expected from the positions of the CpG dinucleotides within the sequence.

Example 4

This example demonstrates the use of methylation-coupled whole genome amplification on DNA recovered from urine samples to increase the amount of DNA available for CpG island marker assays. Urine samples were obtained from 4 patients that were recently diagnosed with prostate cancer. 50 ml samples were spun down at 4000 rpm for 15 min, transferred to 1.5 ml tubes and washed twice with PBS. The DNA was extracted using proteinase K digest (100 μ l of 25 mM Tris pH8.0, 100 mM NaCL, 1% SDS, 5 mM EDTA and 10 μ g of Proteinase K followed by phenol/chloroform extraction and ethanol precipitation. The DNA was resuspended in 10 μ l TE8 buffer (10 mM Tris, pH 8.0, 1 mM EDTA).

A partially random primer with the sequence GGGN₆ (50 ng) was added to 5 μ l of DNA. 12 μ l of a denaturing solution (50 mM KOH, 0.1 mM EDTA) was added to the DNA/ random primer mix. After a five-minute incubation at room temperature, 12 μ l of a neutralization solution (60 mM Tris (pH 7.5), 50 mM HCl) was added to neutralize the reaction. The DNA/primer mix was denatured at 94° C. for 5 minutes, incubated at room temperature for 10 minutes, and then placed on ice.

The amplification reaction was set up in a final volume of 30 μl. The following reagents were added to give the indicated final concentrations: (a) 1×NEB buffer 2 (1× NEB buffer 2: 50 mM NaCl, 10 mM Tris-HCl, pH 7.9, 10 mM MgCl₂, 1 mM dithiothreitol), 333 μM dATP, dCTP, dGTP, dTTP, 160 μM S-adenosylmethionine, and 10 ng/μl of bovine serum albumin (BSA) were combined and to which was added (b) DNA methyltransferase enzyme 1 (0.15 units/μl) (New England Biolabs) and incubated at 37° C. for 10 minutes, and followed by (c) adding Klenow polymerase to a final concentration of 0.167 units/μl, and Klenow exo- to a final concentration of 0.167 units/μl (New England Biolabs).

The reaction was incubated at 37° C. for 16 hours, and the reaction was stopped by the addition of EDTA to a final concentration of 5 mM, phenol/chloroform extracted, and ethanol precipitated. The DNA was resuspended in 40 µl of TE8 and 41 were separated on agarose gel to verify the presence of DNA.

5 The DNA was treated with sodium bisulfite and analyzed by methylation specific PCR as described in Example 1 using the GPR147 and RET assays. The presence of a band of the expected size for either marker indicated the methylation of the associated marker in the input DNA.

All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

The use of the terms "a," "an," "the," and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary lan-

guage (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. It should be understood that the illustrated embodiments are exemplary only, and should not be taken as limiting the scope of the invention.

SEQUENCE LISTING

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360

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The invention claimed is:

1.A method of determining the methylation status of one or 20 more CpG islands indicative of prostate cancer in a human male undergoing prostate cancer evaluation, which method comprises:

isolating or amplifying genomic DNA from a biological sample from a human male undergoing prostate cancer 25 evaluation; and

assaying the genomic DNA for methylation of one or more CpG islands including a CpG island in SEQ ID NO: 49 or SEQ ID NO: 50 associated with NODAL,

wherein the presence of the methylation of the one or more 30 CpG islands, including the CpG island associated with NODAL, is indicative of prostate cancer.

- 2. The method of claim 1, wherein the method further comprises assaying the isolated or amplified genomic DNA for methylation of one or more CpG islands associated with 35 HEMK1, GPX7, PALD, or FGF20, and wherein the presence of the methylation of the one or more CpG islands associated with HEMK1, GPX7, PALD, or FGF20 is indicative of prostate cancer.
- 3. The method of claim 1, wherein the method further 40 comprises assaying the isolated or amplified genomic DNA for methylation of CpG islands associated with HEMK1, GPX7, PALD, and FGF20, and wherein the presence of the methylation of the CpG islands is indicative of prostate cancer.
- **4.** The method of claim **1**, wherein the method further comprises assaying the isolated or amplified genomic DNA for methylation of a CpG island associated with at least one gene that is known to be methylated in prostate cancer and that is known not to be detectably methylated or methylated at 50 a lower level in benign prostate hyperplasia (BPH), and wherein the presence or increased methylation of the assayed CpG islands is indicative of prostate cancer.
- 5. The method of claim 2, wherein the method further comprises assaying the isolated or amplified genomic DNA 55 for methylation of a CpG island associated with at least one gene that is known to be methylated in prostate cancer and that is known not to be detectably methylated or methylated at a lower level in benign prostate hyperplasia (BPH), wherein the presence or increased methylation of the assayed CpG 60 islands is indicative of prostate cancer.
- 6. The method of claim 4, wherein the CpG island associated with at least one gene that is known to be methylated in prostate cancer and that is known to be unmethylated or methylated at a lower level in BPH is or includes one or more 65 CpG islands associated with glutathione S-transferase P1 (GSTP1), glutathione peroxidase 3 (GPX3), cyclin-depen-

dent kinase inhibitor 1C (CDKN1C/p57), or G-protein coupled receptor 62 (GPR62).

- 7. The method of claim 4, wherein the CpG island associated with at least one gene that is known to be methylated in prostate cancer and that is known to be unmethylated or methylated at a lower level in BPH includes a CpG island associated with glutathione S-transferase P1 (GSTP1).
- 8. The method of claim 1, wherein the method further comprises assaying the isolated or amplified genomic DNA for methylation of at least one CpG island associated with a gene selected from the group consisting of kinesin family member 13B (KIF13B), neurogenin 3 transcription factor (NEUROG3), L-threonine dehydrogenase (TDH), N-acylsphingosine amidohydrolase (acid ceraminase) 1 (ASAH1), Kinesin family member C2 (KIFC2), GDNF family receptor alpha 1 (GFRA1), Dickkopf homolog 2 (DKK2), Ras association (Ra1GDS/AF-6) domain family 5 (RASSF5), tumor necrosis factor superfamily member 11 (TNFSF11), and leucine rich repeat containing 49 (LRRC49), and wherein the presence of the methylation of the CpG islands is indicative of prostate cancer.
- 9. The method of claim 4, wherein the method further comprises assaying the isolated or amplified genomic DNA for methylation of at least one CpG island associated with a gene selected from the group consisting of kinesin family member 13B (KIF13B), neurogenin 3 transcription factor (NEUROG3), L-threonine dehydrogenase (TDH), N-acylsphingosine amidohydrolase (acid ceraminase) 1 (ASAH1), Kinesin family member C2 (KIFC2), GDNF family receptor alpha 1 (GFRA1), Dickkopf homolog 2 (DKK2), Ras association (Ra1GDS/AF-6) domain family 5 (RASSF5), tumor necrosis factor superfamily member 11 (TNFSF11), and leucine rich repeat containing 49 (LRRC49), and wherein the presence of the methylation of the CpG islands is indicative of prostate cancer.
- 10. The method of claim 8, wherein the method comprises assaying for methylation of CpG islands associated with at least 7 genes.
- 11. The method of claim 8, wherein the method comprises assaying for methylation of CpG islands associated with at least 8 genes.
- 12. The method of claim 8, wherein the method comprises assaying for methylation of CpG islands associated with at least 9 genes.
- 13. The method of claim 1, wherein the assaying for methylation of a CpG island comprises amplifying a target sequence that includes a CpG island in SEQ ID NO: 49 or SEQ ID NO: 50.

- 14. The method of claim 8, wherein the assaying for methylation of the at least one CpG island associated with a gene comprises amplifying a target sequence that includes at least one CpG island in sequence selected from the group consisting of (a) SEQ ID NOs: 7 or 8 [KIF13B], SEQ ID NOs: 13 or 14 [NEUROG3], SEQ ID NOs: 35 or 36 [TDH], SEQ ID NOs: 43 or 44 [ASAH1], SEQ ID NOs: 119 or 220 [KIFC2], SEQ ID NOs: 123 or 124 [GFRA1], SEQ ID NOs: 129 or 130 [DKK2], SEQ ID NOs: 133 or 134 [RASSF5], SEQ ID NO: 196 [TNFSF11], and SEQ ID NO: 198 [LRRC49], and (b) fully or partially methylated sequences of (a).
- **15**. The method of claim 1, wherein assaying the genomic DNA for methylation comprises terminator-coupled linear amplification.
- **16**. The method of claim **1**, wherein assaying the genomic DNA for methylation comprises using methylation-sensitive restriction endonuclease.
- 17. The method of claim 1, wherein assaying the genomic DNA for methylation comprises differential methylation hybridization.

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- **18**. The method of claim **1**, wherein the amplification of genomic DNA comprises methylation coupled genomic amplification.
- 19. The method of claim 1, wherein assaying the genomic DNA for methylation comprises quantitative PCR.
  - 20. The method of claim 1, wherein assaying the genomic DNA for methylation comprises sequencing.
  - 21. The method of claim 1, wherein the biological sample is whole blood, blood plasma, or blood serum.
  - 22. The method of claim 1, wherein the biological sample is urine
  - 23. The method of claim 1, wherein the biological sample is prostate tissue.
- 24. The method of claim 2, wherein the method comprises assaying the isolated or amplified genomic DNA for methylation of one or more CpG islands in SEQ ID NO: 17 or 18 [HEMK1], SEQ ID NOs: 125 or 126 [GPX7], SEQ ID NO: 15 or 16 [PALD], or SEQ ID NO: 39 or 40 [FGF20], and wherein the presence of the methylation of the one or more CpG islands associated with HEMK1, GPX7, PALD, or FGF20 is indicative of prostate cancer.

* * * * *